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ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 35 (O.S., Vol. XL) AUGUST, 1951 NUMBER 2

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Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1936.

ANNALS OF
INTERNAL MEDICINE

VOLUME 35 AUGUST, 1951 NUMBER 2

THE PATIENT AND THE PHYSICIAN *

By SIR JOHN PARKINSON, M.D., F.R.C.P., F.A.C.P. (honorary),
London, England

PATIENTS will take precedence over physicians in my address, as in natural and chronologic order they do. There would be no physicians if there were no patients, and it is evident that the two groups do not see themselves as the others see them; so it is well to recognize the difference in their outlook. It will be a personal aspect which is presented to you, and my field in medicine, though large, has been circumscribed, so that I have less claim than some to the full title of physician. That cannot be so true today, when you have generously welcomed me and admitted me to your Fellowship. Still, you will notice that my remarks arise from the standpoint of a consultant, and that in a limited sphere.

Let us look at some of the peculiarities of patients, their frailties and their faults, as we think. You must have been struck by their preoccupation with causes. Formerly it was the doctors who ascribed ill-health to ill-doing or to externals; now it is the public. A physician is intent on the diagnosis, while a patient bothers about the cause and thinks it logical to do so. A particularly enjoyable meal is readily accepted as the cause of a heart attack, or it is overwork that brought it about. Though inseparable from human life, anxiety or worry is held to account by the public for heart affections of every kind; and even inside the profession there is a tendency to force this fancy. Nursing a sick relative does not injure the heart, though the nerves may not be equal to it. When war bombing stopped in Britain I did not notice the fall in the incidence of heart attacks which this misconception about causes might have led me to expect.

Dire effects from prolonged physical exertion are also still feared by the public, though not by the profession, which no longer accepts as valid such terms as "athlete's heart" or "strained heart." Likewise, one particular act of exertion may be blamed for a heart attack, even though it was

* Convocation Address, Thirty-second Annual Session, American College of Physicians, St. Louis, Mo., April 11, 1951.

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performed hours or even days before. Mackenzie's dictum may be repeated: the heart does not remember. Physicians should know best the causes of illness, because they have studied pathology and the lay public has not. You know of the pathologist in the postmortem room who said that he was not surprised at what people died of, but he was surprised at what they could live with!

Leaving causes, my impression is that patients incline toward a somber prognosis; against their will, they harbor undue apprehensions and pass from anxiety to fear. Fear has no part in the normal equipment of a physician, still less of a surgeon, but its depth and extent among patients are not sufficiently realized. It is seen in the reaction of the public to heart affections, which they persist in regarding as peculiarly dangerous to life. The truth is that there are only a few varieties of heart disease which carry the risk of sudden death. Not only the risk but the resultant disability are constantly exaggerated. Following a coronary thrombosis, a man will inquire about a further attack; if not, he and his relatives constantly think about it, and, in fairness, they should be told that it is unlikely to happen, though not impossible. Many patients, a few months after such an attack, are able and wise enough to forget about it. There exists, too, the unjustified idea that exertion in cardiac cases must be restricted because it entails danger. Modern medical opinion allows children with congenital malformations of the heart to participate in any and every form of activity which they can undertake without distress. It does them good, not harm, and these children will not hurt themselves. Many adults might follow with advantage the same rule in regard to their handicap.

There has been a change in the relation of doctors to growing children, who no longer fear their doctor any more than they do a London policeman. In my student days there was nothing of the present wholesome attitude of treating them as full, though youthful, human beings. Not long ago an American mother sent her daughter of 14 in alone to consult me, clearly to promote her self-reliance; and already her poise was delightful to witness. An English boy from Eton came in similarly and made me feel quite at ease, so much so that for once I ventured to ask what he intended to be. He replied—with his national humility—"an ambassador."

Certain broad changes have taken place in the attitude of patients to doctors in my time. They no longer mind having them young; experience tells less and modernity more, though they are not always wise in their preference. Up-to-date methods of investigation, often suspect by patients in the past, are now welcomed, nay, demanded. The masterly inactivity sometimes advised in my youth is no longer permitted, even in Britain. Indeed, the expectation, the plea that something shall be done often places the doctor in a predicament. The patient and his friends beseech him to prescribe some new remedy that they have heard about or seen pushed by

specious advertisement, one in which he himself has no faith or which might be harmful.

Many other foibles are encountered in our practice. The real reason for a consultation may not be disclosed; it may be prompted by some fear: a near relative has died unexpectedly, or the patient has been rejected for insurance or for war service, or the papers that he reads have been extra full of mortalities. Even though he may have some disturbing symptom, or be aware of a real and recent heart attack, a wily fellow may keep silent about them in order to get reassurance, and may resent interrogation. To this extent he classes himself with the passive patients of the veterinarian! Then there is the knowing patient full of his own ideas on medical subjects. To one such I said, "You ought to have been a doctor," and you may like his reply, as I did: "A doctor! I've troubles enough of my own!"

Another matter on which patients and physicians do not always see eye to eye is the relative importance of maintaining or restoring health. Many patients will accept treatment, placing all responsibility on the doctor, but shudder at the idea of any moderation on their part. The low value placed on health until sickness comes is astonishing, and some people even then hesitate to pay the necessary price for it. Surely, in the troubled days in which we live, health is all the more precious because so many things have fallen in value. You cannot devalue health.

There is a well-known saying within the profession, "Never believe what a patient says the doctor said," for doctors are habitually misquoted. "He gave me only a year to live" comes from someone who likes to disparage doctors—perhaps one in particular. More truthful was the vigorous man who came to me punctually on the tenth anniversary after a physician had told him that he was "good for another 10 years."

Time and inclination prevent me from talking about certain neuropaths who waste so much of our time. The older and reprehensible habit of despising these unfortunate people and disclaiming responsibility for them has ceased, largely through the advocacy of our colleagues in psychology. But physicians do not count them among their favorite patients, even when remunerative. Yes, it must be conceded that we have our favorites, those to whom we constantly refer as good patients. I suppose the good patient is one who trusts and accepts the diagnosis of his doctor and, on the important things, closely follows his advice, even if now and then a trifle rebellious. Only the best will keep faith when things go wrong, and what a stimulus that firm trust then can be. Confidence is the hallmark of the good patient. A coster in East London, begging me for relief from his trouble, suddenly interposed, "You're my friend if you're a doctor, aren't you?"

Should not something be said in praise of patients? That would be a generalization indeed, and worth little as a tribute from the profession. Yet I feel confident that many of you perceive what I should like to be able to say; we are daily reminded of the dignity of man as man. Physicians see

their patients as they are, faced with the reality of their ill-health; and, though some disappoint, most display the resilience and fortitude which betoken character, and make us respect the human spirit contending with and rising above its physical infirmities. We come to perceive that it is the individual we have to deal with, and that his disease is no more than a circumstance. One must not exaggerate in this respect today, when great and more powerful remedies are in our hands, and their skilful application is the supreme duty of the physician. Yet the bulk of our practice consists not in curing people but in caring for them. To return to my theme, I have never got over my wonder at the way patients "take their medicine" in the bitterest sense of that word—their matter-of-fact acceptance of the disability and frustration caused by illness, and their bearing under pain. What has been publicized in regard to the courage of the wounded soldier in wartime is witnessed by us in everyday practice without comment. Yet not without effect, for there is nothing more appealing and invigorating to the physician. Occasionally one hears this admiration of a patient voiced by a nurse or a colleague, but in general it is observed in silence. During the war attending our clinic each month was a youth of 20 who for years had been watched and shown to students for his cyanosis and clubbing and who could not walk far. We found on inquiry that he filled a steady engagement locally as a first-aid instructor, holding classes during the bombing period. A blue man, scarcely a blue baby! Have you been given by a woman a clear account of her attack of coronary thrombosis at night, but she wouldn't waken her husband? Certainly many a patient has told me that he did not send for a doctor for such an attack at night, knowing the doctor was overworked; and medical men have often said to me, relative to night work, "My patients are very considerate."

How afraid we are nowadays of being sentimental, that is, of showing sentiment or feeling. The fear of it can be carried too far—it is a matter for each to decide—but we cannot allow the public or our patients to believe that as a profession we are unfeeling. Laymen incline to imagine that a medical training produces an indifference to suffering, a hardness of heart, but nothing is farther from the truth. Of all people, a medical man must not wear his heart on his sleeve, but in the presence of sickness he may prove to be the only practical sympathizer about. For that is a privilege of his calling; he is literally in his element.

Before we take a look at physicians from the inside, we might glance at them as they stand in public estimation. Comments about doctors over the ages are, for the most part, unflattering. You will recall many epigrams and verses expressing sarcasm and ridicule of doctors, and few their praises. "God heals, and the physician hath the thanks." "A lucky physician is better than a learned one." "Some doctors take life very easily." Nor do we forget the woman in biblical history who "had suffered many things of many physicians, and had spent all that she had, and was nothing bettered, but rather grew worse."

Apart from sneers about ignorance, and ability to kill rather than to cure, it is noticeable how often greed in doctors is pilloried. Bernard Shaw, a reckless cynic towards doctors, said, "Nothing is more dangerous than a poor doctor." As this is a recurrent and contemporary gibe, it behooves us to guard against even the appearance of this evil. Nothing will undermine the confidence of the public so much as the conviction that we are mercenary. Our services are priceless in a sense, but our patients have a right to fair terms, in keeping with public and professional standards of value.

Favorable quotations, however, may be found in literature more often than in epigram. There is time only for one such, taken from Hutchison and Wauchope's "For and Against Doctors." In "Bleak House," by Charles Dickens, the doctor's wife speaks: "I never walk out with my husband, but I hear the people bless him. . . . I never lie down at night, but I know that in the course of that day he has alleviated pain, and soothed some fellow-creature in the time of need. . . . Is not this to be rich? The people even praise me as the doctor's wife."

It might be said that the public do not think about the medical profession as a whole. They do notice that there is continuity and some solidarity in the profession, I believe, and value the safeguards imposed upon entrance and the standards thereafter required of qualified medical men and women. Fashions in medicine tend to shake the steady trust of the public in the profession; new drugs and new operations may be introduced, some of which prove to be worthless or worse. They are rightly impressed by the remarkable therapeutic discoveries of our time, and these perhaps elevate medicine in public esteem more than anything. But, in the main, people reach their opinion by the demeanor and the character of the individual doctors whom they happen to meet, and by what they gain from those they know and consult.

What a position I now find myself in, daring to remark upon the faults of physicians, of whom I am one, and presuming to advise! Constant vigilance is required to prevent our own personal interests from intruding into our work. A courteous or a talkative patient will sometimes inquire about ourselves and our personal affairs, but we must not be led away too far or too long from his sole purpose in coming. A friend of Stephen Paget said, "I don't want my doctor to talk to me about the National Gallery." At a consultation I have seen a doctor pick up and read a newspaper, apparently forgetting what is exclusively in his patient's mind. I myself have displayed too great interest in the pictures on the wall, or in a charming garden. It is, of course, well to discover and share in our patient's other interests, but we must keep first things first and make it clear that we are doing so.

The truthfulness of doctors is not quite proverbial, and the blatant question is sometimes asked, Should doctors tell the truth? A French cynic has said that women and doctors alone know how necessary and beneficent

to mankind is the lie. The facts are that in clinical science there is devotion to truth and conformity to scientific standards as scrupulous as anywhere, but in practising the art truth has often to be softened. As with medicine, a patient should get as much as is good for him. Truth can be a terrible thing; and we will continue in our good tradition of tempering— but never, I hope, falsifying—truth to those whom we serve. Many people do not want and many cannot take the whole truth. If a patient unfeignedly insists, it is his human right, and he must be told.

A proper measure of unpalatable truth is justified to discipline a patient resisting treatment. For instance, a thumb held long enough on his dropsical ankles may suffice. But it is unjust to intimidate a patient by enlarging his danger or his disability. I used just now the word "discipline" in its sadly outworn sense; the point, however, was made long ago by Francis Bacon: "Physicians are some of them so pleasing and conformable to the humour of the patient as they press not the true cure of the disease."

Silence is golden, but not always in physicians, whose silence may often do far more harm than speech. Silence gives consent, and it may be consent to the fears universally felt by people who are ill. Put yourself in the patient's place—and some day you may have to. Patients resent the omission of any clear statement of what is the matter and what should be done about it, and they go away and say, "My doctor told me nothing." There are constant complaints that a physician does not fully and fairly express his opinion and advice at the end of a consultation. This is every patient's due; the formal and technical report should be for his doctor.

Undue silence often means a want of imagination, and it weakens our usefulness, so we should all master a verbal therapy calculated to allay fear and restore self-confidence. The Hippocratic oath does not include a vow of silence.

On some subjects it is difficult to speak, yet not quite fair to keep silent. To the ordinary physician, for example, sex seems just another part of the human make-up. Its organs serve a natural and healthy instinct and are prone to disease like the others. Some schools of modern psychology may attach to it a rather excessive significance. Perhaps some physicians tend to be too reticent and unapproachable on this particular matter. Cardiac patients often wish to know, though sometimes hesitate to ask, if any restrictions are necessary on their marital relations. I do not refer to those who seek some excuse for evading them, or those too ill to care. Men and women with a cardiac disability do not thereby lose their manhood or their womanhood. It is sometimes part of our office to anticipate a patient's fear or his wife's, and it may be asserted that, provided there is no distress, no special risk is attached. It is a truism that friendship should be cultivated and renewed, and this also applies to full communion between man and wife. Our firm purpose should be to ensure that a patient has confidence to live as full a life as is possible, and we may as well disown the idea that love-making is the worst possible thing for the heart.

Has the profession at large been influenced enough by the awakening of thought and the freedom of discussion on psychology which obtains today? Everyone seems to know a lot about it, and only in that sense do I know anything about it. It appears to me strange that its influence has not been felt more by physicians dealing primarily with organic disease in patients whose minds are normal. They are not called to treat psychoneurotic or psychotic patients. Similarly, few psychologic physicians have close experience of ordinary patients with organic disease. How, then, can we learn to apply modern ideas—insofar as these seem trustworthy enough to be applicable—in dealing with the minds of our patients sick in body? True, there is a wealth of tradition and experience and common sense in daily use with this object. But how can this be blended with the more recent knowledge of body and mind relationship? I am raising this question, not answering it. Those who plan medical teaching have taken action in respect of students in training, but there are those of us with minds less flexible toward new ideas. Let me give an example of the problem. There is the shock of learning that the heart is unsound, especially if it is driven home by an anginal attack; the anxiety and the frustration, present and foreseen, which affect personal, financial and professional plans and prospects. It all hurts long after the pain has been subdued. Maybe the figure of death appears before the sufferer from time to time.

You may say, yes, they need relief of pain, adequate rest and routine medical treatment. A moment's reflection on the nature of the pathologic lesion will convince us of the hollowness of any claim to treat it directly or adequately. Cure is clearly not the word, but care and good management. Adjustment is required, first to the idea of the disability, then to the disability itself. We have to conceive what passes through the mind of the patient. It is the unknown he fears most; we know and should tell him. Words of inquiry, explanation, advice and reassurance are demanded, not so much the old and arbitrary restrictions. That is why I exposed the fault of silence, silence consenting to fear. A flood of questions, doubts and fears rises to the mind of the patient and his friends. We have need of a deeper, more scientific comprehension of them and their consequences. His life may have to be re-planned, certainly readjusted, for it may be shortened. What of his finances? What will be his capacity for work? Has he a dependent wife and family? What about play, exercise, travel? He feels unsafe; who shall give him back his self-confidence? An early rule is to avoid hasty decisions; one doctor patient managed to sell his practice before I could stop him. Retirement should never be advised without serious deliberation. The enforced rest gives time for reflection on both sides, and many difficulties will solve themselves by trial and others by the passage of time; but my point is that the whole problem is our responsibility as physicians, arising as it does from the ill-health of the patient. We must see him through.

In conclusion, the common duty required of a physician lies in the recognition and treatment of disease. If he enlarges his study to cover life as affected by disease, and masters the psychology of the individual sick in body, he will widen his usefulness and reach a fuller life himself as a physician. He will dare to enter into the mind of his patient with imaginative sympathy, proving himself a friend in need. To professional skill he will join human warmth and understanding. By so doing, and only by so doing, will he accept the whole burden and fulfill his destiny. If anyone seeks happiness, here it may prove to be. It is the second mile enjoined in the text, "And whosoever shall compel thee to go a mile, go with him twain." The good physician will accompany his patient on the second mile—and to the end of the road.

ALLERGY IN THE AGED*

By RICHARD A. KERN, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

THIS discussion of allergy in the aged is justified by a number of reasons. There are differences in the incidence of the various kinds of allergic diseases and at times also differences in the clinical pictures of the same disease in the old as compared with younger patients. Chronicity is a major characteristic of allergic disorders in the elderly. There are significant differences in etiologic factors and in non-allergic complications encountered in the aged with allergic conditions. It is harder to find in advanced years the specific causes of allergic disease because of the diminished or lost reactivity of the skin to test materials. Geriatric allergy therefore presents special problems both in diagnosis and treatment. The rapidly increasing proportion of the aged in our population reminds us more and more forcibly of the growing importance of these problems.

There are certain basic principles of clinical allergy which will help us to understand more clearly the facts of allergic diseases in the aged and which therefore deserve emphatic mention.

1. The allergic individual has an inherited, an inborn defect: the ability to become sensitive to substances in his environment with greater ease than can the average individual. He is born that way and he so remains until he dies. Therefore, throughout his life it is possible for him to develop new sensitivities: once allergic, potentially always allergic.

2. That to which he becomes sensitive (the antigen) and the part of him that becomes sensitized (the shock organ) are matters of circumstance and environment, of conditioning and exposure. Since such circumstances and exposures vary with his years, it is understandable that the aged allergic is likely to become sensitive to those things which advanced years bring into his environment and to show that sensitivity in the organs which those years make more vulnerable.

3. A specific sensitivity, say to a pollen or a food, tends to have a limited duration. While it may last for years or even for life, it more often tends to disappear after a few years, especially if during that time the antigen be avoided. As the layman would say, the allergic individual can "outgrow" a particular sensitivity. Therefore the pattern of sensitivities in that individual is a changing thing throughout his life.

4. Allergic diseases are more often due to multiple sensitivities, than to a single one, unless there be daily or constant exposure to the single cause, such as wheat or house dust. It is easier for a person to recognize the rela-

*Read at the 32nd Annual Session of the American College of Physicians, St. Louis, Missouri, April 10, 1951.

From the Division of Medicine, Temple University Hospital and Medical School.

tion between a cause and its effect when a single antigen brings on symptoms, and therefore to escape symptoms by avoiding that antigen.

5. Allergic diseases usually begin in early life because the circumstances, notably excessive exposure, are more likely then to set the stage for sensitization to develop. But they could begin at any time of life, or they might never begin, if the stage were never set for their inception, even though the person by inheritance was of allergic strain. Homologous twins, if of allergic heredity and raised in the same environment, develop the same types of allergic disorders and at about the same age. But if raised in different environments, their allergic experiences will also differ, and as much as do those environments.

6. The allergic (sensitizable) nature of any person, be he old or young, is established by a clinical history of disorders obviously due to allergy, and, in the absence of such a history, may be suggested, although not proved, by a positive family history of allergy.

In the light of these principles let us now examine the data on allergic disorders as observed in the aged.

Allergic diseases in general are less frequent in the elderly than at a younger age. The aged tend to lose sensitivities of earlier years and to acquire fewer new ones as they grow older. This is due to several possible reasons: the usual tendency of sensitivities to lessen in severity and to drop below the threshold for producing symptoms; a natural desensitization or hyposensitization by repeated small exposures to the antigen; a lessened exposure to potent allergens in the more sheltered existence of later years; the increasing ability of an allergic person to recognize new sensitivities early and so to avoid their incitors.

Certain allergic diseases are decidedly less frequent in old age. This is particularly true of some of the more acute types, such as hay fever and allergic migraine, and of the food allergies. The elderly patient has come to know and avoid his enemies, so that allergic headaches and digestive symptoms due to hypersensitiveness are decidedly less common. Contact dermatitis is less frequent because of the less varied and less intense, or wholly lacking occupational exposures.

The important differences in the clinical manifestations of allergy in the aged as compared with the younger have to do with changes in structure and function of certain tissues incident to aging and with the types of antigens that assume greater importance in the aged. Chiefly to be stressed, therefore, are the allergic diseases of the skin and the respiratory tract and the greater frequence of sensitivity to drugs.

The skin loses much of its capillary bed, its fatty panniculus diminishes and its sweat and sebaceous glands are undernourished, atrophy and in part disappear. As a result the skin is dry, pale, and cool, and its blood supply less adequate not only for heat regulation but for reparative processes in case of trauma and infection. The circulation may be further impaired in some

areas by varicose veins and by arterial inadequacy. Such skin is therefore more vulnerable to the effects of soap, detergents, irritants, trauma and infection. Minor lesions, instead of healing promptly, become the sites of protracted mycotic and bacterial infections. As a result, *allergic pruritus* is frequent in aged allergic patients. This often progresses to an *allergic eczema,* which in turn may be complicated by a fungus sensitivity (dermatophytid).

Contact dermatitis, while less frequent in the aged, is nevertheless an important problem because of its severity and its stubborn resistance to treatment. It has been said that one-third of a dermatologist's office practice is accounted for by contact dermatitis, chiefly from cosmetics. Old women contribute more than their share of such cases from the use of scalp lotions and tonics, pomades, hair dyes, wave sets, face powders and rouges, nail polishes and lacquers, antiperspirants, deodorants, depilatories, "anti-wrinkle" creams, massage creams and many other things too numerous to mention. In both men and women the local use of ointments, usually as prescribed by the physician, can be responsible for a contact dermatitis on top of the eczema which the salve was supposed to cure. Such a contact dermatitis does not necessarily remain localized at the first site of exposure. It often becomes generalized and may reach a serious exfoliative stage that takes a severe toll of the patient's strength and can threaten life itself.

At this point the greater incidence of *drug allergy* in the aged should be mentioned. Those policy holders of the Metropolitan Life Insurance Company aged 65 and over have an average of 35 days of disabling illness per year as compared with 6.9 days for all policy holders.[1] Obviously the aged receive much more medication than do younger persons. Much of that medication is parenteral. Moreover, gastric anacidity, which is present in 30 per cent of those over 65, probably facilitates sensitization by the oral route. Many of the newer drugs are proving to be potent antigens. It is therefore not surprising that drug allergies are not only more frequent in the aged but are actually on the increase.

A generation ago, quinine, ipecac, aspirin and the arsenicals headed the list of drug allergens. Phenolphthalein, the commonest of laxatives, now holds high rank. The serious reactions to gold in arthritic patients are on an allergic basis. Many drugs in current use have at times induced a sensitivity. But all of them have been far surpassed both in the frequence and in the severity of their allergic manifestations by the sulfonamides and the various antibiotic agents. Penicillin sensitivity is rapidly increasing at all ages, thanks to its routine use in every minor infection. What is more important, in addition to the mild reactions noted during the early years of penicillin therapy there are now an increasing number of serious and even fatal reactions. This may be due to the fact that more and more people are getting third and later courses of the drug. I also have the decided impression that the use of depot types of penicillin is producing more frequent and more serious allergy.

The pattern of drug allergy may be changing, or at least is being recognized in broader scope. The commonest forms are still the urticarial, erythematous or eczematous skin reactions, rarely purpuric or exfoliative. Severe or fatal neutropenia is less frequent because of awareness of its causes and their consequent avoidance. But sharp reactions of the serum-sickness type of picture, with urticaria, fever, leukocytosis, eosinophilia and joint manifestations are decidedly on the increase. Some of these cases become more chronic and merge into *periarteritis nodosa*, a commonly fatal disease that is certainly on the increase and more so in older patients. I particularly recall several such cases in physicians who knew themselves to be of allergic tendency, yet who treated themselves for simple colds with sulfadiazine or penicillin, and died as a result.

Perennial allergic rhinitis is the commonest manifestation of allergy in the respiratory tract. It is also the most important, not because of its own symptoms, which may be trifling, but because it is the commonest precursor of that much more serious disease, especially in the aged: asthma. Perennial allergic rhinitis is also the most neglected and worst treated of respiratory allergies. It is commonly so mild that its victims do nothing about it in its early stages when diagnosis and treatment are simple and curative. Not until secondary infection in the paranasal sinuses or nasal mucous polyps have complicated the picture, do most patients seek relief. Then all too often the treatment consists of unwise surgical attention to these complications, while the underlying allergic state is ignored. The physician often overlooks the condition, because he fails to ask about it and because the old patient doesn't bother to mention it, since he has come to take his sneezes, rhinorrhea and nasal blocking for granted. Yet the very antigens (usually inhalants) that have for years produced the nasal symptoms, are often the same ones that eventually cause the asthma: attention to these antigens would have cured the rhinitis and prevented the asthma. (I have published elsewhere the data to prove these points.[2])

Asthma is the most serious of respiratory allergies, and particularly so in the aged. Chronic respiratory infection and consequent bacterial allergy are frequent in those with perennial respiratory allergic disease. Chronic infection causes the ciliated epithelium of the bronchi to be replaced with squamous cells, and so impairs an important mucosal function. Emphysema, mild bronchiectasis and poor circulation further emphasize the burden of the disease upon the patient. As a result, asthma in the aged is more often continuous and chronic, and infection tends to dominate its clinical picture: chronic cough, purulent sputum, low-grade fever, exacerbation of asthma in the wake of acute colds.

Now I wish to state a seventh in the series of basic principles of clinical allergy with which I began this discussion:

7. Skin reactivity to test materials is greatest in childhood, lessens in adult years, and is often lost in old age, even though the shock organ itself

may still react strongly with symptoms on exposure to the antigen. For example, feathers can cause asthma in a patient whose skin gives a negative test reaction. Skin tests are therefore less and less reliable in aging patients to determine the causes of their symptoms.

In consequence, an unfortunate and largely erroneous concept has arisen: that asthma can be classified as either *extrinsic,* that is, due to allergens outside the body, or *intrinsic,* due to causes within the body, notably infection. The common failure to find positive skin reactions in elderly asthmatics and the frequence of chronic respiratory infection in these patients have led to the wrong assumption that asthma which begins in late life is practically always *intrinsic,* infectious, non-allergic in origin. (Thus, Rackemann [3] has long claimed that extrinsic asthma seldom begins after the age of 45.)

This is far from the truth. Sensitivity to external allergens, if properly and thoroughly sought for, can be established as a factor in the majority of patients whose asthma begins in old age, and should be suspected in the rest. A frequent mistake is to assume that a patient whose asthma began in advanced years is probably not an allergic individual and therefore not requiring study for possible sensitivity. Yet questioning the patient whose asthma began at 70 will often uncover a long succession of other manifestations of allergy, beginning with eczema in infancy, hay fever and urticaria in adolescence, and perennial nasal symptoms (for example, sneezing habitually six or more times in a row) that have existed many years before the asthma started and may even have been due to the same antigens that now affect the bronchial tree in addition to the nose. The frequent and the extremely important rôle of infection in the asthma of the aged is not denied, but its *sole* responsibility is seriously to be questioned.

It is beyond the scope of this paper even to list, let alone discuss, the possible manifestations of allergy in the aged. However, there should be mentioned a few because of the frequence with which in practice they are overlooked.

Chronic cough without wheezing is at times on an allergic basis. The suspicion of an underlying sensitivity should be aroused if the cough is unproductive, if it tends to be paroxysmal and to recur under certain conditions, and if the patient gives a personal or familial history of allergic disease.

In patients with obvious cardiac disease and circulatory failure, an allergic (asthmatic) component is easily overlooked. Yet the relief of the allergic factor by avoiding its antigenic cause can do more to help an overburdened circulation than can all the other therapeutic measures at our command. The possibility of an allergic factor in such a patient may be suggested by the paroxysmal nature of the cough, by the finding of wheezing expiratory râles, rarely by the finding of an eosinophilia, and often by the prompt relief which epinephrine gives. In cases of *paroxysmal auricular tachycardia,* it should be remembered that about 25 per cent of them are on an allergic basis.

Episcleritis and corneal ulcer, frequently recurring, are likely to be due to allergy. *Involvement of the eye-lids* in a dermatitis should point to cosmetic or other contact allergy. *Pain in the eye-ball,* recurring over the years and without any demonstrable objective findings, may be the equivalent of an allergic migraine.

Allergic epilepsy is rare at any age, and especially so in the aged. But its commonest cause when it does occur in the elderly is sensitivity to tobacco. *Meniere's syndrome,* on the other hand, occurs with greater frequency in later years, and in 20 per cent of cases is on an allergic basis. The results of treatment in the allergic group are far superior to those in all the rest.

The diagnosis of allergic disease in the aged calls for greater care and skill than at any other time of life.

Skin tests, including patch tests, are less reliable in the elderly, but are by no means useless. Any test reaction which differs even slightly in degree from that of the control must be noted. Such slight reactions may have the greatest clinical significance as proved by relief of symptoms on avoidance of the substances in question, and by provocation of symptoms on exposure to them. Lest such slight reactions be overlooked, the tests must always be read by good daylight, never by artificial light.

Contrary to general opinion, an allergist is not just a skin-tester: technicians can be trained to perform that task. His function is to determine the causes of trouble in the light of his experience with, and knowledge of allergic diseases, not merely by skin tests, but by history and observation, including the device of the diary of symptoms and exposures, and so to lay the basis for proper treatment.

But the greatest emphasis must be placed on the completeness of diagnosis and the consideration of the patient as a whole. For the older the patient, the more certain are there to be encountered the organic and the functional disorders that aging inevitably brings.

The *treatment* of allergic disorders in the aged likewise demands in full measure the best application of the physician's art and science. It is clear that treatment must be suited to the whole patient, not merely to an allergic disease.

From the standpoint of *allergy,* the principles of treatment include: (1) complete avoidance of avoidable antigens (any food, most inhalants); (2) as good as possible a partial avoidance of those not completely avoidable; (3) hyposensitization by injection of extracts of the unavoidable antigens (a few inhalants).

From the standpoint of *infection,* one must (1) treat infected foci that require it; (2) immunize the patient, as well as may be, with proper (usually autogenous) vaccines; (3) treat him with the antibiotics and chemotherapeutic agents that the proved susceptibilities of his bacteria indicate; and (4) protect him against infection, at times by recourse to climatic therapy, a device more applicable in the aged than at any other time of life.

To these must be added the judicious use, for symptomatic relief, of various measures well known to you. Such symptomatic treatment is of course only palliative, and must always be subordinated to truly curative measures.

All of this is so obvious that it scarcely needs saying. But there is currently in vogue a method of treatment that tends to ignore these principles, in the long run to the detriment of the patient. I refer to the use of ACTH and cortisone.

These substances have indeed proved to be the most potent means to stop an allergic reaction, almost regardless of its cause or of the shock organ involved. They have therefore proved invaluable in the relief of symptoms of chronic or severe allergic disorders and in many instances have been life-saving.

But the fact remains, they do have limitations. They are palliative, not curative; they relieve symptoms but they do not alter the underlying sensitivities. Therefore a relapse of the allergic disease occurs when there is adequate exposure to the offending allergen.

Now if the allergen is known, as for example, the cosmetic that precipitated a serious contact dermatitis, then ACTH or cortisone may well be used to stop the dermatitis, and it need never recur if that cosmetic be avoided thereafter. In such cases these substances are in effect curative and find their clearest indications.

But if the allergens are not known, as for instance in an asthmatic patient whose sensitivities and complications have never been explored, the use of ACTH or cortisone brings about a relief that can not be maintained with any certainty. Indeed, the patient may be left at a disadvantage by their use. The relief which cortisone gives in asthma is often only partial as well as transient. The hypoplasia of the adrenal that follows its prolonged use puts the patient in a worse state than he was before. This is proved by the fact that in a patient only partly relieved by cortisone, ACTH is unable to bring relief for several weeks after the cortisone was stopped: it takes that long for the adrenal to regenerate. ACTH usually gives complete relief from asthma for weeks to many months. But the basic sensitivity remains, and so relapse can and does occur. What is worse, ACTH is itself a good antigen: if after weeks or months a second course is tried, it may find the patient now highly sensitive to ACTH and cause a severe, even fatal reaction. Cortisone, praised by some as non-antigenic, has only recently been reported to have caused sensitivity that stopped its further use.

There are yet further reasons for caution in the use of these agents in the aged. Recognized contraindications include hypertension, edema, circulatory failure, active infection, peptic ulcer, mental depression or other psychopathic tendency, hypercholesterolemia, atherosclerosis, and the danger from the increased coagulability of the blood produced by these agents in precipitating vascular accidents in brain or heart. Old age itself is a relative

contraindication, since the incidence of unfavorable side-effects is distinctly greater in those over 50. ACTH and cortisone can truly be life-saving in severe asthma, but their routine use in asthma in general, and especially in aged asthmatics, is to be condemned. They are emergency weapons, to be used with full knowledge of their dangers, and only after other measures have failed.

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NOCTURNAL DISORDERS OF MEDICAL INTEREST *

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"Watchman, what of the night?" Isaias Ch. 21, Verse 11.

THERE are many diseases, symptoms and syndromes that tend to occur frequently, predominantly or even exclusively during the night. Classification of these disorders and elucidation of the mechanism responsible for their nocturnal predilection are both a challenge and an interesting mental exercise. Even though these disorders may appear at times to be linked somewhat loosely, and to hang together by a tenuous thread, the temptation to treat them as a group is nonetheless strong. To quote H. Selye [1]: "From time to time we feel the urge to reorganize our classifications in medicine, even if nothing really new is added—just as we rearrange the contents of our desk drawers. It gives us a chance to eliminate the useless objects and to put the most useful over into the accessible positions. It may even call to our attention some long forgotten item which we banished into obscurity at a time when we failed to realize its now so obvious utility."

Night has many well known attributes—darkness, moonlight, starlight, to name but a few. It is also associated with certain events and phenomena, some sanctioned by nature, others by custom, the most important being sleep. Night and day, sleep and wakefulness are rhythms common to all humanity.

What is sleep? Despite the extensive amount of work that has been done in the attempt to clarify its nature, sleep still remains a mystery. Many theories have been put forth since the dawn of history.[2, 3, 4, 5, 6, 7] The ancient Greeks, from Alcmaeon to Aristotle, explained sleep as a retirement of the blood from the brain to the larger vessels, and awakening as its return to the brain. During the Middle Ages, superstitions about sleep abounded. Modern times have seen the birth and death of many concepts. The following is a brief summary of some of the theories:

The biochemical theories explain sleep by the cortical effects of accumulated noxious substances, e.g., lactic acid (Pearson), hypnotoxin [4] (Pieron), acetylcholine (Dikshit).

According to Howell's theory of cerebral ischemia, peripheral vasodilatation caused by the fatigue of the vasomotor center results in shifts of blood to the extremities, leaving the brain in an ischemic state. The ischemia brings about sleep.

The theory of internal inhibition (Pavlov [5]) regards sleep as a result of spread of internal inhibition over the cerebral cortex. Customary hour, customary preparations, repeated movements, monotony, all serve as conditioning stimuli.

* Received for publication July 17, 1950.

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As to the hypothalamic theories: Experimental as well as clinical evidence has recently revealed the all important rôle of the hypothalamus in the causation of sleep. The exact mechanism, however, is controversial. Hess [6] believes that there exists in the hypothalamus a "sleep center," the stimulation of which causes sleep. Kleitman [7] postulates the existence in the hypothalamus of a "wakefulness center." Wakefulness, according to him, is a hypothalamic function, whereas supplementary wakefulness of choice, as well as the diurnal sleep-wakefulness cycle, is a cortical function. The "wake center" in the hypothalamus requires for its proper functioning the stimulus of cortical activity. The latter, in turn, is maintained by afferent impulses from proprioceptors, especially in muscle. If these impulses are reduced, the cortex becomes inactive and fails to stimulate the hypothalamic "wake center," and sleep ensues. Muscular relaxation is thus a necessary prelude to sleep. Sleep may also result from "blockage" of afferent impulses anywhere between the hypothalamus and the cortex. This concept renders homage to both the hypothalamus and the cortex.

Thus the nature of sleep still remains a mystery. The phenomena of sleep, i.e., its physiologic accompaniments, however, lending themselves, as they do, to direct observation and study, are somewhat better known and understood. But even here the picture is incomplete, and some aspects are controversial.

The following phenomena have been observed during sleep:

Fall of blood pressure, 10 to 30 mm.
Sudden rise in blood pressure during vivid dreams.
Slowing of pulse rate, 10 to 30 beats per minute.
Vasodilatation.
Increased activity of vasomotor reflexes.
Increased secretion of sweat.
Decreased lacrimal and salivary secretion.
Slight slowing of respiration.
Relaxation of muscles.
Diminution of somatic reflexes.
Fall of basal metabolic rate, 10 to 15 per cent.
Depression of heat regulating mechanism.
Decrease of urine volume and increase in its specific gravity.
Increased CO_2 tension in alveolar air and arterial blood, with resulting tendency to acidosis.
Decrease in the production of 11 oxysteroids.

Many of the above phenomena are manifestations of depression of vital functions and overactivity or uninhibited activity of the parasympathetic nervous system.

In addition to the above processes, one or more of which may be factors in the causation of disorders of function, there is an important postural

factor in sleep, that of recumbency. The horizontal position, universally adopted by sleepers, entails complex cardiovascular and respiratory adjustments, e.g., increase in venous return, increase in cardiac output,[8] increase in blood volume [9] and decrease in vital capacity.[10, 11]

Sleep has also important psychic components. Dreams, nightmares, hypnagogic hallucinations are as much a part of sleep as is restful repose. These psychic phenomena have a pronounced effect on somatic function, especially blood pressure. It has been observed that during a vivid dream with a strong emotional content, the blood pressure may rise as high as 200 mm. MacWilliams,[12] who made a thorough study of the cardiovascular effects of sleep, arrives at the following conclusions: "It is clear that the foregoing facts must be taken as profoundly modifying the simple conception of the night as the time of rest, and sleep as a condition in which quiescence prevails. . . . This conception, while true as regards undisturbed or sound sleep, has to be qualified by the consideration that night and sleep are occasionally the season of acute reflex and emotional disturbances which, in the peculiar conditions present induce very pronounced strain on its weak points, whether these be cardiac with susceptibility to fibrillation or arterial with risk of rupture."

No less important than the psychic concomitants of sleep are those of nocturnal wakefulness and semi-wakefulness. Fears, frustrations, anxieties and worries that are suppressed during the day rise to the surface during the interregnum between sleep and wake, or during the waking hours of the night, to torment their victims. The background of tranquillity and the air of unreality accentuate the broodings of the introspective. The immediate and ultimate effects on the mental and physical health of the indivual may be profound.

Thus postural, physiologic, biochemical and psychologic factors may be instrumental in precipitating the disorders that stalk the night. Even though the modus operandi of these factors may often be obscure, and more than one of them may be implicated in each case, they can still serve as a convenient basis for classification. Nocturnal disorders may thus be grouped, according to the predominant factor involved, into those due to: (1) postural factors, (2) vasomotor factors, (3) neuromuscular factors, (4) biochemical factors, and (5) psychological factors.

The only important representative of the first group is paroxysmal nocturnal dyspnea. The clinical picture of this dramatic manifestation of left ventricular failure is well known. The patient wakes with a sense of anxiety, respiratory distress and suffocation. He sits up fighting for breath. He often gets up seeking the window for more air; after a varying interval he coughs up some blood-stained mucus, feels relieved and returns to bed. Recumbency acts mainly by causing gravitational shift of blood from the splanchnic area and lower extremities to the thorax, thereby intensifying pulmonary congestion. The increase in blood volume that occurs in the horizontal position may be a contributory factor. The increase in cardiac

output in recumbency may play an important part. Neurogenic reflexes arising in the failing left ventricle may be the mediating mechanism of pulmonary congestion.[13] The mechanical effect of a raised diaphragm, interfering with pulmonary ventilation, also enters the picture. Sleep, too, contributes to the pulmonary congestion by virtue of the diminished irritability of the respiratory center. The resulting decrease in the responses of minor adjustments, e.g., the quickening of respiration or change in posture that normally takes place in the waking state, allows pulmonary congestion to proceed unhindered until it is too late.

The second group comprises many diverse disturbances of function, determined to a large extent by the nature of the underlying vasomotor mechanism. The latter may be one of sudden rise of blood pressure and increased heart action accompanying a vivid dream, or one of generalized vasodilatation of quiet sleep due to the fatigue of the vasomotor center, or one of some unknown disturbance of vasomotor control.

Cardiovascular stresses, already referred to, evidenced by the rise of blood pressure and increased heart action during the restless sleep, may be the precipitating cause of hemorrhages—pulmonary, cerebral, gastrointestinal—and of sudden death. To quote MacWilliams again: "The individual may, during the nocturnal period of assumed repose, be subjected to suddenly developed stresses, as estimated by the rise of blood pressure and the evidence of increased heart action far beyond what is involved in ordinary muscular exercise gradually initiated. . . . Thus hemorrhages . . . and other disturbances in the night can be readily accounted for; also sudden death, probably due to ventricular fibrillation."

Vasodilatation is a major factor in the nocturnal intensification of pain and paresthesia, especially sensation of heat in various neuritides, whether due to vitamin B deficiency, diabetes mellitus or alcohol, and in vasomotor disturbances such as erythromelalgia, trench foot, immersion foot and causalgia. Vasodilatation, with resulting heat, probably also accounts for aggravation of pruritus and pain during the night in many diseases of the skin. Whether it plays a part in the causation of nocturnal pains in neoplastic and inflammatory diseases of bone is questionable.

That to the above list of nocturnal disorders with a strong vasomotor component may be added acute gout is a view advanced by Frederic Wood Jones.[14] Himself a sufferer from the disease, he is of the opinion that the active process precipitating acute gout is the irregular spasmodic action of the vasomotor nerves controlling the arteriovenous shunts of the periarticular plexuses. This concept, although constituting a departure from the traditional "biochemical" theories, which attempt to explain gout and all its manifestations on a metabolic basis, is noncommittal with regard to the ultimate constitutional and metabolic background of the disease, and only concerns itself with the acute gouty attack, which usually begins and attains its maximal intensity during the night.

Unlike gout, the articular pain of other arthritides is not usually predominantly nocturnal. There are, however, cases in which nocturnal pain, the so-called "vesper" pain of arthritis, is the main feature of the condition. In these cases, it is thought that the aggravation of pain is due to the removal of the splinting action of muscles guarding the joint, consequent upon their relaxation. These cases would thus come within the orbit of the third group (neuromuscular factors). To the latter probably also belong the interesting syndromes affecting the upper extremities—scalenus anterior syndrome, cervical rib, and brachialgia paresthetica nocturna. The latter, also known as paroxysmal arm dysesthesia, deserves special mention because, unlike the others which also occur during the day, it is exclusively nocturnal. It is a form of acroparesthesia occurring in middle aged women, and is characterized by pain and numbness in the ulnar distribution of the hand and forearm which wakes the patient from her sleep and disappears after movement. There are no objective signs, and the course is benign. The likely mechanism in this condition and in the nocturnal accentuation of the pain of cervical rib and scalenus anterior syndrome is that of compression of the lower part of the brachial plexus through relaxation of the muscles of the shoulder girdle, with the resulting depression of the shoulder.[15]

In contrast to the generalized muscular relaxation characteristic of sleep, and yet possibly its indirect effect,[16] stand out the localized nocturnal muscular spasms, usually of the muscles of the calf, that often afflict elderly and middle aged people and occasionally young men.[17] These night cramps present a fairly typical picture. It is usually that of a middle aged or elderly person who, on awakening, is seized by a cramp in one or both calves. The calf muscles are tender and contracted. Application of heat, massage or vigorous movement help to relieve the spasm. Avoidance of stretching the foot may prevent it.[18]

The cause of these cramps is not known. Gootnick [16] believes that they are "a lasting tetanic contraction of a muscle group due to reflex bombardment of the myoneural junction by a stream of impulses from some neighbouring source of irritation." He attributes the nocturnal incidence of the spasms to the fact that during sleep there is a relaxation and lengthening of muscle. This lengthening constitutes a trigger mechanism which throws it into a spasm, a mechanism identical with that of a stretch reflex and based on the same physiologic principle, that the tension of muscle fibers increases as the muscle lengthens and, beyond a certain degree of lengthening, muscle acquires a tendency to recoil into spasm.

Other theories have been advanced in an attempt to explain the nocturnal cramps on a biochemical basis. The calcium deficiency theory has largely been abandoned, since repeated investigations failed to detect any abnormalities in calcium metabolism during the night. That accumulation of metabolites due to vascular stasis in the inactive muscles may be a factor

is a view still favored by some.[19] If true, it would bring this condition within the range of group 4 (biochemical factors).

Biochemical factors and their endocrine control are probably active behind the scenes without being obvious in many nocturnal disorders. They are, on the other hand, quite conspicuous yet poorly understood in others. Examples of the latter are gout, paroxysmal nocturnal hemoglobinuria and idiopathic familial periodic paralysis.

Gouty arthritis, with its nocturnal onset and maximal nocturnal intensity, has already been referred to in connection with the vasomotor theory of its causation. The latter, however, has not as yet gained wide acceptance. Old and new theories are competing strongly. Deserving of special attention are the observations made by Wolfson.[20] He noted that, in gout, the normal ability of the organism to respond to 11 oxysteroid lack by an increase in their production is impaired. This lack, according to Wolfson, precipitates the acute attack of gouty arthritis. He attributes this failure of 11 oxysteroid production to the anterior pituitary, which fails to release the extra ACTH. The ultimate locus of disturbance is probably in the hypothalamic control of ACTH release. The fact that 11 oxysteroid production has been noted to be decreased during the night,[21] and the possible close relationship between sleep control and ACTH release, both functions vested in the hypothalamus, may give a clue to the mystery of the nocturnal onset of the gouty attack.

No less mysterious than gout is the rare syndrome of paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli). In this condition, paroxysms of intravascular hemolysis, with resulting hemoglobinemia and hemoglobinuria, frequently occur during sleep. It has been observed that the erythrocytes of subjects suffering from the disease are abnormally susceptible in vitro to hemolysis in plasma of increased acidity. Hence it is assumed by many authorities [21, 22, 23] that the increase in the acidity of the blood during sleep, especially in areas of the body where circulation is relatively inactive, such as the spleen, is the precipitating cause of the attacks. This view, however, is disputed by other workers who fail to find significant changes in pH during sleep. That some as yet unknown changes in the concentration of inorganic ions in the blood, rather than acidity, may be the important factor has been suggested by Marks.[25] Thus the mechanism of nocturnal intensification of hemolysis in this condition still remains a mystery.

Another syndrome with a biochemical background is idiopathic familial periodic paralysis.[26, 27] This rare condition, transmitted as a familial trait, usually manifests itself at or after puberty, and is characterized by recurrent attacks of flaccid paralysis of skeletal musculature, loss of deep reflexes and preservation of sensation and mental function. The attacks come on during sleep without warning and last from a few hours to a few days. The characteristic finding during these episodes is a low serum potassium. This is

apparently not due to excessive excretion of potassium, but to its entry into the intracellular portion of body tissues. There are also changes in phosphorus and creatine metabolism in this disease. The exact rôle of potassium and the locus of the defect responsible for the paralysis, as well as the association with sleep, are as yet unknown.

The above condition should not be confused with the entity known as "sleep paralysis." [28] The latter is a transient benign paralysis at the beginning and end of sleep, which is associated with a clear consciousness, lasts a few seconds or minutes and is terminated by contact. It is a common symptom in the narcolepsy-cataplexy syndrome,[29] but may exist as an independent condition, not infrequently in psychoneurotic subjects. Although its mechanism is obscure, it can be fitted somewhat loosely into the group of nocturnal disorders (group 5) due to the psychologic concomitants of sleep and nocturnal wakefulness. This group comprises such diverse symptoms as insomnia, delirium, hypersomnia, somnambulism, hypnagogic hallucinations, night terrors, and possibly some neuralgias. Of the latter, proctalgia fugax [30] deserves a passing comment, for it is an exclusively nocturnal symptom. It is a severe high rectal pain, as distressing to the patient as it is puzzling to the physician. Psychogenic factors are also important in every type of pain, paresthesia or any other disturbing symptom intense enough to keep a patient awake. They are all felt more acutely in the night, because of the absence of distracting stimuli of diurnal wakeful activity, and because of the psychologic nocturnal factors, previously referred to, predisposing to introspection.

The conditions discussed above by no means exhaust the list of nocturnal disorders. As examples of important omissions may be mentioned night pain and night secretion by duodenal ulcer, night sweats of tuberculosis, and nocturnal rises of temperature in febrile conditions, especially in children. Nor has the broader aspect of the general pathophysiology of periodicity of disease been gone into. This paper, however, lays no claim to completeness, and it is hoped that those sins of omission have not detracted from its main purpose, which is that of stimulation of interest in the nocturnal periodicity of disease.

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CHLOROQUINE IN HEPATIC AMEBIASIS *

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THE introduction by Conan [1] of chloroquine as an antiamebic agent and his demonstration of its usefulness in hepatic amebiasis established the efficacy of a relatively nontoxic drug in amebic infections of the liver. These observations were soon confirmed by Shookhoff [2] in 12 cases, by Sodeman [3] in two, and by others.[4, 5, 6]

The present report concerns our experiences with the two patients of Sodeman referred to by personal communication by Conan,[1] and with five additional patients. In all, we are reporting seven instances of hepatic amebiasis in which chloroquine was used. These case reports, aside from further confirming the effect of chloroquine in the types of hepatic amebiasis described by Conan, establish its value in other clinical types, and demonstrate also (in three cases) a stage of refractoriness to chloroquine.

CASE REPORTS

Case 1, Recurrent Amebic Hepatitis. A 49 year old white male was admitted to the U. S. Marine Hospital on August 12, 1948, and discharged on September 8, 1948. He had been treated in this hospital in May, 1948, for acute amebic hepatitis (stools negative, complement fixation test positive) with 65 mg. of emetine daily for eight days. Marked improvement had been noted and the patient had been discharged on the eighteenth hospital day. He remained asymptomatic until August 8, 1948, when fever was noted. The next day pain developed in the right upper quadrant and right lower chest. A day later a mild nonproductive hacking cough appeared. Then right lower quadrant pain occurred. There was no diarrhea. On admission the oral temperature was 102° F. (figure 1). Breath sounds were diminished in the right lower chest posteriorly. The right upper and lower quadrants were tender when palpated, as was the edge of the liver. Examination of the chest by roentgen-ray and fluoroscopy revealed an elevated right hemidiaphragm with impaired descent on inspiration. The leukocyte count was 16,650, with 82 per cent neutrophils. Stools were positive for *Endamoeba histolytica* trophozoites and, on sigmoidoscopy, the bowel wall showed lesions typical of amebic ulcers. Liver function studies were normal (cephalin flocculation, negative; thymol turbidity, negative; serum bilirubin, less than 0.25 mg. per cent). Chloroquine (0.6 gm. base daily for two days, then 0.3 gm. base daily) was begun on the third hospital day (figure 1). Symptomatic improvement was dramatic. Liver tenderness entirely disappeared after eight days of treatment. However, stools were still positive for *E. histolytica* trophozoites

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 10, 1951.

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after 19 days of chloroquine therapy. Diodoquin was then started. No parasites were found in subsequent examinations (figure 1). Fluoroscopy showed a freely movable right hemidiaphragm two to four days after the treatment with chloroquine was begun. The patient was still asymptomatic nine months later. The final diagnoses were recurrent amebic hepatitis and acute amebic colitis.

Case 2, Acute Amebic Hepatic Abscess; Acute Amebic Colitis. A 38 year old white male school teacher was admitted to the U. S. Marine Hospital on April 8, 1949, and discharged June 9, 1949. The chief complaints were pain in the right upper quadrant and weakness of seven days' duration. Black loose stools had been present for six days. The patient had had some fever without chills and had been treated during that week for pneumonia. He was acutely ill, mentally confused and dehydrated. Coarse râles were heard in the right lung base, and the abdomen was mildly distended. Tenderness was present over the liver as well as in both lower quadrants. Fluoroscopy revealed elevation and fixation of the right hemidiaphragm. Blood-flecked mucus, obtained at proctoscopy, showed many motile *E. histolytica* trophozoites. Emetine hydrochloride, 65 mg. intramuscularly daily, was begun on the second hospital day. Wangensteen suction was also begun on the second day because of increasing abdominal distention. Little improvement was noted, except in the ab-

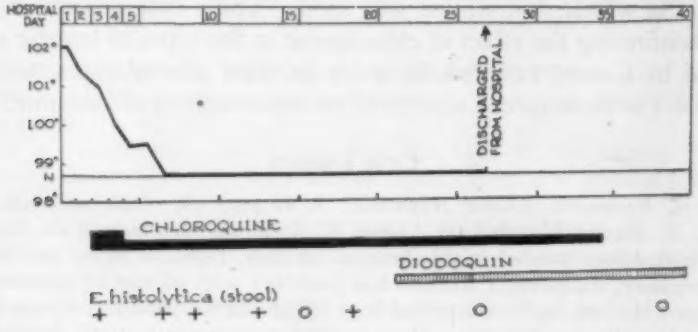

FIG. 1. Case 1.

dominal distention, until, when emetine was discontinued on the seventh hospital day, chloroquine was begun (0.6 gm. base daily for two days, then 0.3 gm. base daily). The temperature approached normal after four days of treatment (figure 2), but on the eleventh day of chloroquine therapy the patient developed cough and pain in the right chest and began spitting dark thick material, characteristic of amebic pus but microscopically negative for *E. histolytica*. The temperature began to rise. It was thought that an amebic abscess of the liver had spontaneously started to drain. Two days later emetine, penicillin and streptomycin were given in addition to chloroquine. The temperature again subsided in three days, the cough became less productive, and from that time until discharge six weeks later the patient steadily improved. At the time of discharge the lung had cleared by roentgen-ray examination and the stools were negative for cysts or parasites.

Case 3, Chronic Amebic Hepatic Abscess. A 23 year old white male was admitted to the U. S. Marine Hospital on May 11, 1949, with a draining abscess of the right lower posterolateral chest wall of three months' duration. In December, 1948, he had had an appendectomy; he had been well until January, 1949, when he had noted fever, malaise and pain in the right upper quadrant. A liver abscess had been drained surgically in February, 1949. This had failed to heal under antibiotic (penicillin and streptomycin) therapy. Emetine had been given without benefit. At the

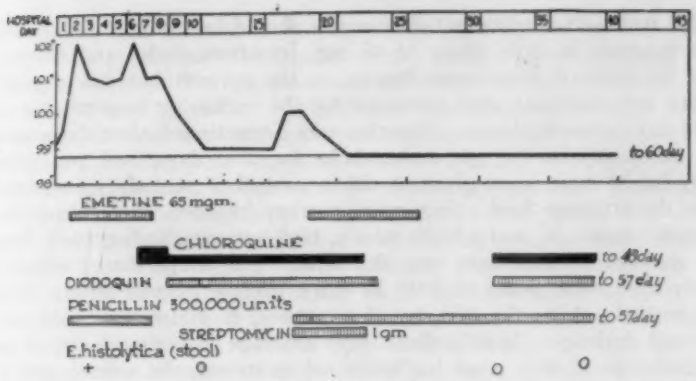

FIG. 2. Case 2.

time of transfer to this hospital on May 11, 1949, the patient weighed 85 pounds (usual weight 135 pounds). He was emaciated and acutely ill. Profuse quantities of reddish brown material mixed with green creamy odorless pus were draining from an opening measuring 1 cm. in diameter in the right posterolateral chest. Surrounding the opening was an ulcer measuring 5 cm. in diameter, with dirty, necrotic, undermined edges. A chest roentgenogram showed an elevated right leaf of the diaphragm without evidence of pulmonary involvement. Motile trophozoites of *E. histolytica* were found in the drainage material. Stools were negative for parasites or ova. The hemoglobin was 7.0 gm.; total serum proteins, 4.36 gm. per cent (albumin, 2.71, and globulin, 1.65 gm.). Bromsulfalein (5 mg. per kilo) showed 12 per cent retention at 45 minutes. The thymol turbidity reaction was 9.5 units; the cephalin flocculation test, 2 plus at 48 hours, and the prothrombin time, 55 per cent of normal. Because of the refractoriness to emetine therapy in another hospital, it

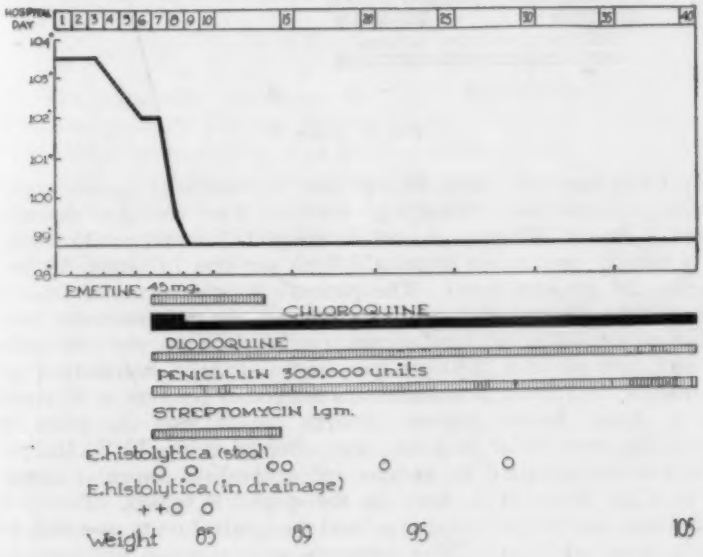

FIG. 3. Case 3.

was decided that both emetine and chloroquine should be administered simultaneously. Therefore emetine, in daily doses of 45 mg. intramuscularly, and chloroquine and diodoquin in standard doses were begun on the seventh hospital day (figure 3). Chloroquine and diodoquin were continued for the remaining hospital stay of 33 days, and for 14 days after discharge. Emetine was discontinued after the seventh day of therapy. Streptomycin, 0.5 gm. twice daily for nine days, and penicillin, 300,000 units daily for 33 days, were given to aid in control of secondary invaders found in cultures of the drainage fluid. Supportive therapy included whole blood transfusions, liver extract, vitamin K, and a high calorie, high vitamin, high protein diet.

The response to treatment was dramatic. The temperature, which had been persistently high, with peaks of 103° F. daily, became normal within 36 hours and remained normal. After the first day of treatment, *E. histolytica* could not be found in the wound drainage. Within three days drainage had almost ceased and, at the time of discharge 33 days after institution of treatment, the wound was closed and epithelized. Local therapy of the wound consisted of saline irrigations and vaseline

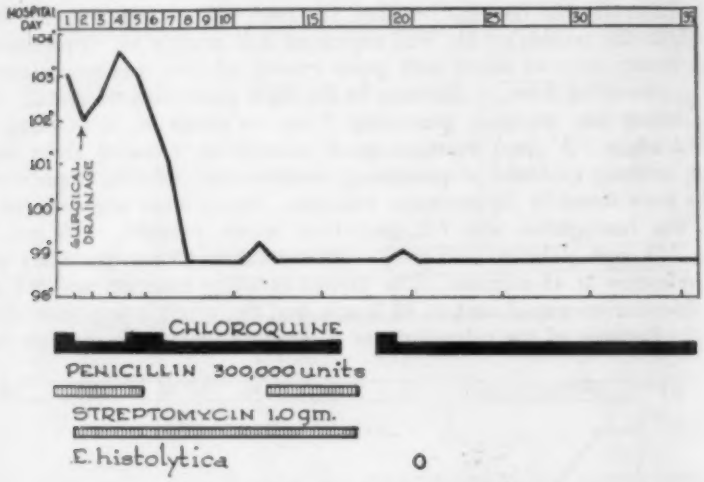

FIG. 4. Case 4.

dressings. Liver function studies 14 days after institution of treatment gave the following results: bromsulfalein (5 mg./kg.) retention, 4 per cent at 45 minutes; cephalin flocculation, 2 plus at 48 hours; thymol turbidity, 15.5 units; prothrombin time, 100 per cent of normal; total serum proteins, 5.9 gm. per cent (albumin, 3.9 gm. per cent, and globulin, 2.0 gm. per cent). The patient's weight increased from 85 to 105 pounds during the 33 days of treatment. After 40 days of treatment, liver function studies showed the following: total serum proteins, 6.28 gm. per cent (albumin, 4.48 gm. per cent, and globulin, 1.80 gm. per cent); cephalin flocculation, plus/minus; thymol turbidity, 18.5 units; bromsulfalein retention, 4 per cent at 45 minutes.

Case 4, Acute Amebic Hepatic Abscess. A 28 year old white male radio operator, having been ill for 36 hours, was admitted to the U. S. Marine Hospital. The onset was characterized by malaise and generalized muscular aches, and was followed in a few hours by a "knot" in the epigastric region. Twenty-four hours before admission, the patient noted fever and the gradual onset of a dull aching pain in the right upper quadrant. Other symptoms were anorexia and some aching pain in the right shoulder. There was no prior history of diarrhea except the day before

admission, when he had three loose bowel movements following a laxative administered by a private physician. On admission, the patient appeared acutely ill. The oral temperature was 103° F.; the pulse was 118, and the blood pressure, 122 mm. Hg systolic and 82 mm. diastolic. No jaundice was noted. The lungs were clear. The abdomen was flat but there was moderate rigidity and marked tenderness in the right upper quadrant. The liver was not palpable. The leukocyte count was 22,400, with 67 per cent neutrophils, 26 per cent lymphocytes, 5 per cent monocytes and 2 per cent eosinophils. The diagnostic impression fluctuated between hepatitis and cholecystitis. Both penicillin and chloroquine diphosphate, 1 gm. daily, were started. Because of signs localizing in the anterior abdomen and of the progressive course, it was deemed advisable on the second day to do an exploratory laparotomy. The dose of chloroquine was reduced to 0.5 gm. daily. At operation, a solitary abscess on the dome of the right lobe of the liver was seen and drained by aspiration. About 30 c.c. of material were obtained and motile *E. histolytica* trophozoites were found. Streptomycin was begun. There was no apparent response to the treatment and on the fourth day the chloroquine dosage was increased to 1.0 gm. daily for two days (figure 4). A marked improvement was noted, and from this time onward the patient's course was uneventful. Stool studies showed no *E. histolytica* cysts or

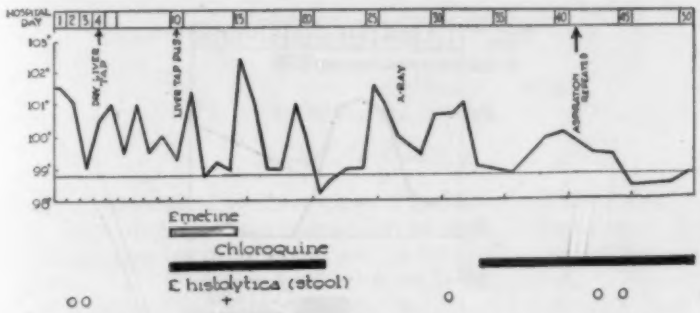

FIG. 5. Case 5.

trophozoites. Ten days after operation the total serum proteins were 3.80 gm. (albumin, 2.10, and globulin, 1.70 gm. per cent). They returned to normal 20 days after operation (total serum protein, 6.53 gm. per cent; albumin, 4.19 gm. per cent, and globulin, 2.34 gm. per cent). Hemogram eight days after operation showed 11.5 gm. hemoglobin and 3,980,000 erythrocytes. This had increased to 14 gm. hemoglobin 10 days later. Liver function tests showed a serum bilirubin of 0.75 mg. per cent, thymol turbidity of 6.5 units, and bromsulfalein excretion (5 mg. per kilo) of 2 per cent in 45 minutes. The cephalin flocculation test was reported as 2 plus.

The patient was discharged as fit for duty December 30, 1949, with instructions to take diodoquin, two tablets three times a day for 14 days. He returned two weeks later for follow-up studies. At this time he felt well and had gained weight. Liver function studies were repeated and again were normal.

Case 5, Chronic Amebic Hepatic Abscess. A 58 year old white male was admitted to the Charity Hospital in March, 1949, with fever, chills and pain in the right upper quadrant. A diagnosis of amebic liver abscess was made. When the abscess was drained, pus containing *E. histolytica* was obtained. The patient was placed on emetine, 1 gr. a day for 10 days, but failed to improve; he was then given chloroquine, 250 mg. twice a day for 12 days, but failed to improve. The fever became low-grade. The patient was difficult to handle and discharged himself from the ward.

When he was readmitted on May 18, 1949, with fever, chills and pain in the right upper quadrant, the same diagnosis was made. On May 21, aspiration was attempted but no pus was obtained (figure 5). On May 27, aspiration was successful and pus was secured. The patient was given emetine, 1 gr. a day for five days, with chloroquine, 250 mg. a day for 12 days. No improvement was noted. On June 20, the dose of chloroquine was increased to 250 mg. twice a day, but no improvement was noted. On June 27 the abscess was again aspirated. The chloroquine was continued and the symptomatic picture cleared entirely.

Case 6, Acute Amebic Hepatitis. A white female, 35 years of age, with a chief complaint of fever, was seen by one of us (W. A. S.). She stated that for several weeks she had felt feverish and tired. Epigastric pain, intermittent in character, developed. There was no vomiting, jaundice or diarrhea. Past history disclosed nothing of moment in reference to the present complaints. Physical examination showed the following: The oral temperature was 99.8° F. and the blood pressure (right arm) was 95 mm. Hg systolic and 60 mm. diastolic. The sclerae were pale. The lungs were clear. The liver was tender and extended three fingerbreadths below the costal margin. The spleen was not felt. There was slight cecal tenderness. The hemoglobin was 10.7 gm. and the erythrocyte count 4.2 million. The leukocyte count was 13,000, with 88 per cent polymorphonuclear cells. Fluoroscopic examina-

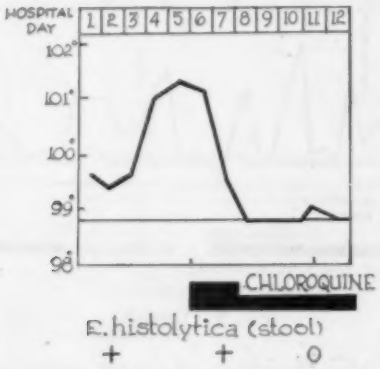

FIG. 6. Case 6.

tion showed a normally placed right diaphragm, with some impairment of motion on deep inspiration. Stools were positive for *E. histolytica* cysts. Sigmoidoscopic examination disclosed normal findings.

Chloroquine diphosphate was started, with a daily dose of 2 gm. in divided doses for the first two days and 1 gm. daily in divided doses on subsequent days (figure 6). Within two days, liver tenderness was diminished and the liver border started receding. The patient became asymptomatic. Chloroquine was continued until the seventeenth day. A course of diodoquin was then started. Subsequent follow-up (six months later) showed the patient to be asymptomatic and free of *E. histolytica*.

Case 7, Acute Amebic Hepatitis. A 40 year old white male was seen privately by one of us (W. A. S.) in August, 1949. He had been well until one month previously, when he began to lose appetite and to develop weakness which forced him to stop his occupation as a shrimper. Epigastric pain developed, especially to the right of the midline and particularly after heavy meals and at night. He often felt feverish and would awaken at night in a drenching sweat. He felt chilly at times but had no frank chills. There was no cough, nausea or diarrhea.

Examination showed a man in a poor state of nutrition, with a blood pressure

of 134 mm. Hg systolic and 76 mm. diastolic. The oral temperature was 99.8° F., the pulse 76 and the respirations 20. In the right upper quadrant a tender liver extending two fingerbreadths below the costal margin was palpated. The right diaphragm appeared elevated, and this finding was confirmed by fluoroscopic examination. The leukocyte count was 11,000, with 82 per cent polymorphonuclear cells. The erythrocyte count was 4.2 million and the hemoglobin 12 gm. Bromsulfalein retention was 0 per cent at 45 minutes. The thymol turbidity was 2.8 units and the cephalin flocculation 1 plus at 48 hours. A complement fixation test on serum taken on admission was subsequently reported as positive. Cultures and agglutinations for Weil's disease were negative. *E. histolytica* cysts were present in the stools.

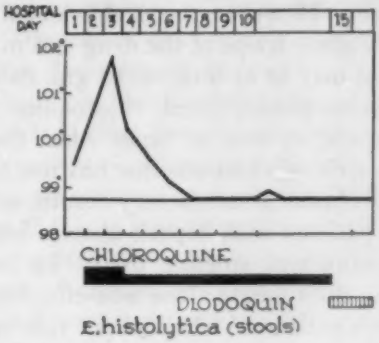

FIG. 7. Case 7.

The patient was started on chloroquine, 2 gm. daily in divided doses for two days, followed by 1 gm. daily in divided doses for 14 days. On the fourth day of chloroquine the temperature began to recede, and on the sixth day of chloroquine it reached normal (figure 7). The liver tenderness had disappeared. The liver was then palpable one fingerbreadth below the costal margin, and within the next two days it was no longer palpable. The patient was discharged to his home on the sixteenth day. A course of diodoquin was prescribed. Follow-up studies for one year showed no recurrence.

DISCUSSION

The therapeutic schedules used in our seven patients were essentially variants of that described by Conan.[1] In four instances results were prompt and dramatic; in three instances they were not.

Conan recommended a primary, or loading, dose of 0.6 gm. of the base (1.0 gm. of chloroquine diphosphate) daily for two days, followed by 0.3 gm. (0.5 gm. of the diphosphate) daily for two or three weeks. Basnuevo and Gutierrez Estarli [4] used a schedule of 0.01 gm. of the salt per pound up to 100 pounds of body weight daily for three days, followed by 0.01 gm. per pound up to 50 pounds body weight daily for 24 days. In their hands this schedule was entirely successful, and at times entailed the use of doses smaller than those advocated by Conan. Emmett [6] used 0.5 gm. daily with success.

Four of our seven patients followed the course of prompt recovery with chloroquine therapy described by Conan and others.[1, 2, 4, 6, 7] Our patients 1, 6 and 7 had amebic hepatitis, two being of the acute and one of the re-

current variety. Patient 1 received the doses recommended by Conan, while patients 6 and 7 received double this dosage. It appears that the higher doses used in patients 6 and 7 were unnecessary and that a smaller dosage might have been just as effective. In the cases reported in the literature which were similar to these patients, results have been as dramatic as those obtained in our own group. Since chloroquine in the doses used produces only minor toxic symptoms, a reduced schedule is not important from that standpoint. Occasional nausea, vertigo, headache and disturbed ocular accommodation are the chief manifestations, and these occur on the reduced schedule as well. However, the establishment of a minimal effective dose would eliminate needless waste of the drug and might possibly minimize toxic effects. The dose may be as little as 0.5 gm. daily.

In some of the reports already cited, chloroquine has been described as effective in amebic hepatic abscess, at times when the patient has been refractory to emetine as well as when emetine has not been used.[8] Basnuevo and Gutierrez Estarli [7] obtained satisfactory results with chloroquine locally and by mouth in four patients with hepatic abscess which had been drained. In none of these patients was emetine used. In two patients with pulmonary manifestations, chloroquine alone was effective.

In one of Basneuvo's patients' [8] who had not received emetine, the wound did not heal for 80 days, and closure occurred only after 25 gm. of chloroquine diphosphate, in three series of 9, 7.5 and 8.5 gm. each, had been given. In this instance we wonder if the addition of emetine might not have hastened recovery. Our patient 3, who had a chronic draining abscess and who failed to respond to emetine, promptly improved and the wound closed under chloroquine. However, in this patient emetine was given along with chloroquine, a procedure not followed in Murgatroyd's patient, who was given chloroquine only after termination of emetine therapy, as reported by Conan.[4] Conan's figure 6 indicates that this patient had been given emetine for 19 days by various routes (for the first 10 days by subcutaneous injection in 60 to 90 mg. doses daily, by mouth during the second five days, and by continuous irrigation into the abscess cavity from the tenth to the nineteenth day) before chloroquine was started. Apparently the first dose of chloroquine was given about 20 days after the last day of intensive emetine therapy, both by mouth and by injection, and about 10 days after the last local application of emetine. Surely emetine was still present in the patient at the time chloroquine was started, for the excretion of emetine is slow. Emmett's patient,[6] who cleared entirely on chloroquine, apparently had received emetine orally for several weeks at a time, but the timing of this therapy is not clear.

In one patient who had a perforated abscess,[9] Basnuevo and Vazquez Rosales found improvement with emetine, but 15 days later the wound was still open and draining a sanguineous secretion in which amebae were not demonstrated. Chloroquine caused clearing and healing of the wound in eight days. Such instances suggest that the combination of emetine and

chloroquine may, at times, be important to recovery. None of the reported cases and none of our own settles this point. More data are necessary.

In the patient just cited, chloroquine did not produce the dramatic results seen in our cases 1, 6 and 7, and the same is true in our patient 2. The exhibition of chloroquine in standard doses, including a loading procedure, appeared to produce some initial beneficial effect and then the symptoms recurred. Apparently an abscess ruptured into a bronchus on the eleventh day of chloroquine. The addition of emetine, penicillin and streptomycin to the chloroquine therapy then produced results but confused the picture as far as drug response was concerned. The events at this time cannot be precisely interpreted. The patient did "escape" from control on chloroquine and, had the chloroquine dosage been increased without addition of other procedures, we would have had some helpful data. However, emetine and antibiotics were added. It is clear that chloroquine alone in the doses given was not adequate. In patient 4, after surgical drainage of a liver abscess containing *E. histolytica,* no response was obtained to 0.5 gm. of chloroquine daily. However, when the dose was raised to 1.0 gm. daily for two days, an effect was noted on the fifth day. Here the results might be interpreted as a response regardless of change in dosage. However, in view of the results in patients 6 and 7, some response might have been expected before this time.

Patient 5 also failed to respond to 0.5 gm. daily. Even with drainage, emetine and 0.25 gm. of chloroquine, no improvement was obtained, but when the dose was again raised to 0.5 gm. and further aspiration done, therapy was successful. In this patient we again see failure to respond to chloroquine until an additional procedure (drainage) was carried out. This patient is similar to Manson-Bahr's.[8]

These results show the importance of multiple factors in successful therapy and indicate that diagnosis by therapeutic trial with chloroquine may not be feasible, for failure to respond to chloroquine does *not* rule out amebic hepatic disease. In one instance 0.5 gm. was not effective and in one 0.25 gm. was not. Our patient 5 failed to respond to chloroquine on two occasions, once after emetine and once after emetine and drainage. While both our case 4 and Conan's case 8 were refractory to emetine, our patient 5 was refractory to both drugs in two instances. As with emetine, negative therapeutic tests must be interpreted with caution. Certainly the dose schedule recommended by Conan seems generally satisfactory. If there is no response the dose may be increased, as in our patients 6 and 7, before the drug is considered a failure, and even then, if there is no response, the drug may be found to act later when other therapeutic procedures are added. These procedures are at times determinants of the effectiveness of chloroquine, just as they are with emetine.

Thus, the present series of seven patients not only further confirms the reports of others of the effectiveness of chloroquine in hepatic amebiasis but

extends the observations to acute and recurrent abscess and indicates also that at times chloroquine, as is true with emetine, may not be efficacious without other procedures.

In all instances the patient was finally given, in addition to chloroquine, one of the drugs (diodoquin, milibis, chiniofon) known to be effective in colonic amebiasis. This was done because of the known inefficiency of chloroquine in colonic amebiasis and because of the importance of the removal of the original focus.

Many patients have hepatomegaly with colonic amebiasis.[10] General evidences of infection (chills, fever, leukocytosis) are absent. The liver is tender on palpation. Since hepatomegaly may result from many causes, its association with colonic amebiasis is not diagnostic of hepatic involvement with *E. histolytica*. The frequent disappearance of the hepatomegaly when colonic amebiasis is treated with amebacides known *not* to be effective in hepatic amebiasis suggests an association with the colonic amebiasis either by low-grade involvement with *E. histolytica* (true amebic hepatitis) or by a secondary change of some type. In one instance of this type, biopsy of the liver disclosed the presence of *E. histolytica* and suggested actual involvement of the liver parenchyma with *E. histolytica* but to a degree which is reversible if the feeding focus in the colon is removed.

In the present series, no such instances of "simple" hepatomegaly are included. One of us (W. A. S.) has used chloroquine in the treatment of a number of patients having colonic amebiasis and hepatomegaly. A disappearance of the hepatomegaly occurred, but since we have obtained the same results with milibis, diodoquin and other drugs effective in colonic amebiasis, and since the classification of the hepatic process in these patients is in doubt, these cases are not included here.

Conclusions

The effectiveness of chloroquine in hepatic amebiasis has been clearly confirmed. Primary failure of the drug in three patients with subsequent success establishes the fact that this drug, like emetine, is not always effective, and that a failure to respond to therapy is not necessarily an index of nonamebic hepatic involvement.

Refractoriness to chloroquine in certain stages of hepatic abscess is described. Later, the drug was effective.

No evidences of serious chloroquine toxicity were noted in this series of seven patients.

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ELEVATED SERUM PANCREATIC ENZYME VALUES WITHOUT PRIMARY INTRINSIC PANCREATIC DISEASE *

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It has long been appreciated that the Cherry and Crandall [1] modification of the Loevenhart method for determining serum lipase activity, and the Somogyi [2] method for determining serum amylase activity, are valuable laboratory procedures for studying intrinsic pancreatic disease. However, elevations of serum pancreatic enzymes in conditions other than intrinsic pancreatic disease occur. It is the purpose of this paper to review the literature on this subject and to report on 21 cases, all of which showed appreciable elevations of serum pancreatic enzyme activity without intrinsic pancreatic disease.

The normal values of serum amylase and serum lipase determined by the methods referred to above vary with each laboratory. The top normal value in our laboratory for serum amylase is 140 mg. per cent, and for serum lipase, 1.0 c.c. of N/20 NaOH.

In 1932, Cherry and Crandall [3] reported that 78 per cent of the cases of multiple sclerosis studied had elevated serum lipase values. However, in 1937 Swan and Myers [4] were unable to confirm Cherry and Crandall's work. In 1934 Jergesen and Simonds [5] studied the serum lipase value in 50 cases with proved peptic ulcers. Twenty-five normal cases were used as controls. Seventy-six per cent of the peptic ulcers had elevated serum lipase activity, using 0.3 c.c. of N/20 NaOH as the top level of normal, as proposed by Cherry and Crandall.[1] Of this group, four were gastric ulcers, and all of these had greater than 0.3 c.c. N/20 NaOH reading. Of the 25 patients used as controls, three showed levels above 0.3 c.c. N/20 NaOH. One patient had nephrosclerosis and showed a reading of 0.5 c.c. One patient had a possible kink in the right ureter and had an elevation to 0.5 c.c. One patient had diabetes mellitus, pyelitis, nephritis and cystitis, and showed an elevation to 1.2 c.c.

In 1934, Hinton [6] reported 13 cases of duodenal ulcer with an enlarged head of the pancreas adherent to the duodenum. The amylase and lipase determinations in these cases were believed to be too variable to be of diagnostic value. Hurst and Stewart,[7] in a study of peptic ulcers in 233 autopsies, found that the pancreas formed the floor of the ulcer in 24.5 per cent and the liver in 4.2 per cent, while in 183 cases of marginal ulcers the pan-

* Received for publication March 31, 1950.
Material for this paper was compiled while the author was a research fellow in gastroenterology at the Graduate Hospital, University of Pennsylvania. Aided by the Julia M. Keim Research Foundation of the University of Pennsylvania.

creas formed the floor of the ulcer in 19.5 per cent and the liver in 1.5 per cent.

In 1935, Tuchman et al.[8] showed that 10 mg. of mecholyl injected hypodermically into dogs produced a rise in serum amylase from 127 to 1,400 per cent four hours after the injection, while post-pancreatectomy the same dogs, given the same dose of mecholyl, had a rise of 0.0 to 66.0 per cent at the end of four hours. In 1935 Guszich [9] studied the serum lipase values as influenced by operations. He reported that 50 per cent of cases in which an abdominal operation was performed on organs lying some distance from the pancreas showed an elevation of the serum lipase activity, but in none of these cases was the elevation marked. In 30 per cent of the cases of abdominal carcinoma there was an elevated lipase which, in some instances, returned to normal following radical resection or roentgen therapy. The lipase titer was studied in eight cases that had gastric operations during which the pancreas was known to be traumatized. Seven of these eight cases showed elevated serum lipase titers. The rise was present for three days postoperatively and then returned to normal. Cases were studied in which operations on the stomach were performed with no or only minimal pancreatic trauma. The serum lipase rise was minimal or absent in those cases. Following 16 cholecystectomies for cholelithiasis, the serum lipase was elevated in 11 instances (64.7 per cent), in none of which was disease of the pancreas present at the time of operation. It was found that any manipulation of the common duct usually resulted in an elevation of the serum lipase titer. The author felt that positive cultures of *Streptococcus, Staphylococcus albus* and colon bacillus from the gall bladder at operation frequently were associated with elevated serum lipase determinations postoperatively. This elevation occurred in six out of seven cases with gall-bladder cultures positive for these organisms. Guszich hypothesized that the elevations of serum lipase observed following operations on the stomach, duodenum and biliary passages were due to mechanical insult to the pancreas through operative trauma. The question was raised as to whether trauma to the coeliac ganglia might not have been a factor. Guszich emphasized that the lipase determinations were of no prognostic value in any of the groups of cases that he studied.

In 1936 Hashimoto [10] experimentally produced epigastric peritonitis and studied the amylase levels in the urine and serum and the lipase values in the serum. Hashimoto used methods for determining pancreatic enzyme values different from those which we have employed, hence, the two studies cannot properly be compared.

Comfort,[11] using 1.5 c.c. N/20 NaOH as the upper limit of normal serum lipase value, found that in five out of seven cases of duodenal ulcer the serum lipase was elevated. Of these five cases, three had subacute perforations of the ulcer, two into the pancreas and one into the gall-bladder, with associated cholangitis. He also found that five out of 37 cases of hepatic disease

showed elevations of the serum lipase. These five cases were diagnosed as follows: 1) jaundice with Malta fever; 2) hepatitis with jaundice in lobar pneumonia; 3) toxic hepatitis due to cinchophen poisoning; 4) toxic cirrhosis of unknown origin, and 5) biliary cirrhosis. In these hepatic cases, Comfort suggested the possibility of associated pancreatitis, and felt that the serum lipase determination was of no value in studying hepatic disease. Comfort also studied 48 cases of carcinoma of the stomach and found normal serum lipases in all. In a study of 85 miscellaneous cases, only three showed elevations and these were in cases with peritonitis of undetermined etiology, puerperal septicemia and pulmonary abscess.

Cope et al.[12, 13] experimenting on dogs, found that the serum amylase titers increased following hypophysectomy and adrenalectomy, and decreased following pancreatectomy and the administration of insulin.

Probstein et al.[14] in 1939 reported on 17 cases of acute perforated peptic ulcer. Four of these cases had elevated serum amylase levels, with elevations to 600, 214, 200 and 190 mg. per cent, respectively. The case which showed an elevation to 600 mg. per cent was diagnosed as pancreatitis. At autopsy a perforated gastric ulcer was found contiguous with the pancreas. On section the pancreas showed only inflammatory change of the capsule. The authors did not correlate the dates of the determinations with the clinical course of the disease. Thirteen cases of perforated anterior wall peptic ulcers were studied and, of these, four showed normal amylase levels and nine were subnormal. Probstein et al. quoted Walton[15] that 90 per cent of acute perforated peptic ulcers were anterior, and Thompson[16] that 69 per cent of acute perforated ulcers were anterior. From his experience with the above mentioned cases, Probstein believed that a moderately elevated serum amylase titer could be commensurate with perforated peptic ulcer, but that a very high serum titer was indicative of acute pancreatitis.

Dozzi[17] demonstrated that the serum amylase titer could be elevated by producing uranium nephritis in dogs. Nonaka[18] found that the serum amylase determinations were elevated in 17 cases of lobar pneumonia and five cases of influenzal pneumonia. He reported that the serum amylase titer was elevated on the day of crisis and usually remained elevated for 10 to 19 days. Johnson and Bockus[19] reported elevated serum lipase values in intestinal obstruction.

Polowe[20] reviewed the causes of elevation of serum amylase activity in conditions other than those of primary pancreatic disease. He reported that these elevations could be found in: 1) 66 per cent of pneumonias; 2) perforation of peptic ulcer into or near the pancreas; 3) high intestinal obstruction; 4) salivary duct occlusion, suppuration or mumps; 5) impairment of renal function, and 6) adrenal cortical insufficiency in the dog. Fennell[21] reported an elevated serum amylase in all of nine cases of mumps but could not rule out associated pancreatitis. The same author cited 105 cases of pancreatitis of which 11 were complicated by mumps, while in 7,054 cases of mumps, 171 had acute pancreatitis.

Goyena [22] studied the serum amylase levels in relation to diets. The normal for serum amylase values in Goyena's study ranged between 34 and 102 mg. per cent. Goyena found the average serum amylase level on a full diet to be 59.6 mg. per cent, on a protein and fat diet to be 55.2 mg. per cent, and on a carbohydrate diet to be 87.2 mg. per cent. Goyena also studied six patients with chronic lower lesser curvature gastric ulcers. Four of these cases had elevated serum amylase levels to an average of 125 mg. per cent. In these four cases the ulcer extended to the posterior surface of the stomach. He studied 21 cases of duodenal ulcers, of which three had gastrectomies and three showed perforations, two into the pancreas and one into the liver. Ten showed elevated serum amylase levels; of these 10, two were in the gastrectomy patients, one was in the case which had perforated into the liver, and seven were in ordinary uncomplicated duodenal ulcers. Those which had perforated into the pancreas had normal serum amylase levels. The average serum amylase level for the 21 cases studied was 93 mg. per cent. Sixty-six per cent of the lesser curvature gastric ulcers and 47.5 per cent of the pyloroduodenal ulcers of Goyena's series showed elevated serum amylase values. The highest serum amylase value obtained in this series was 212 mg. per cent, and it occurred in a gastrectomy patient. In this series the author did not correlate the dates of the enzyme determinations with the clinical course of the disease.

In 1946 Polowe [23] reported additional cases with elevated serum amylase levels as measured by the cupric oxide precipitation method. These included thrombosis of the superior mesenteric and portal vein, with hemorrhagic infarction of almost the entire small intestine and 1,500 c.c. of hemorrhagic peritoneal effusion, mesenteric cyst, retroperitoneal metastasis from embryonal cell carcinoma of the testes, two cases of pneumonitis, two cases of uncomplicated duodenal ulcer, one case following partial gastrectomy and splenectomy where the stomach was adherent to the pancreas and which developed a postoperative anuria and pneumonia, one case of toxic nodular goiter, and one case of aneurysm of the thoracic aorta.

Our interest in the elevation of serum pancreatic enzymes in instances other than those associated with primary intrinsic pancreatic disease was aroused by a case in whom an elevated serum amylase and lipase level led us to an erroneous diagnosis. This mistaken diagnosis probably caused the death of the patient, a 50 year old colored woman who had been admitted with a history commensurate with partial intestinal obstruction but with equivocal physical findings. The roentgen diagnosis was partial small bowel obstruction. Serum amylase determination on the third day of her illness was 343 mg. per cent and the serum lipase 1.0 c.c. On the fourth day of the illness the serum amylase was 243 mg. per cent and serum lipase 2.5 c.c. After these determinations we considered acute pancreatitis as the diagnosis of choice, with an associated moderate degree of ileus. The patient was placed on a strict pancreatic therapeutic regimen. It is worthy of note that

the blood urea nitrogen on the third and fourth days of illness was 70 and 90 mg. per cent, respectively. We failed to give this the proper attention. On the fifth day of her hospitalization, the patient showed the abdominal signs of generalized peritonitis without an elevation in the temperature or the white blood cell count. The patient was explored on the seventh hospital day, at which time soupy pus was found throughout the abdominal cavity, and the ileum, approximately 15 cm. from the ileocecal valve, was found to be incarcerated and strangulated beneath a band of adhesions. There was a free perforation in this portion of the bowel. The patient died some six hours postoperatively. No autopsy was performed and the pancreas could not be inspected at operation. One might speculate as to the cause of the elevated serum pancreatic enzymes. Three mechanisms could have played a part; namely, the generalized peritonitis with secondary inflammation of the capsule of the pancreas, the impaired renal function with a decrease in the excretion of the enzymes, and partial small bowel obstruction.

About three weeks later a man presented himself at the receiving ward and gave a history and showed the physical findings of an acute perforated peptic ulcer. A roentgenogram for free air under the diaphragm showed none. A stat amylase determination was 326 mg. per cent. Because of the classic history and physical signs, the patient was operated upon and an anterior prepyloric perforated gastric ulcer was discovered and repaired. There were 1,500 to 2,000 c.c. of peritoneal soiling. The pancreas at operation was described grossly as "soft." The serum amylase was normal on the day following operation, but the serum lipase reached a peak of 1.8 c.c. on the fourth hospital day. The diagnostic and prognostic implications of the serum pancreatic enzyme studies in this case are obvious. Acute pancreatitis was a definite differential diagnostic possibility. However, the clinical signs were so classic that the diagnosis of ruptured peptic ulcer was imperative. If they had not been so clear cut we might easily have made the diagnosis of acute pancreatitis and instituted medical therapy instead of recommending the necessary surgical therapy.

Five of the 21 cases of our series had elevated serum pancreatic enzymes in association with perforated peptic ulcers. Four were acute perforations and one was subacute. Three of the five cases had free acute anterior gastric ulcer perforations, one had a subacute pyloroduodenal perforation into the liver, and one was an acute posterolateral perforation of the duodenal cap. The highest amylase determination in this group was 326 mg. per cent, while the highest lipase was 6.2 c.c. We attempted to correlate the serum pancreatic enzyme elevations with the time following perforation. Two of the cases showed elevated readings within the first 24 hours after perforation; two did not show an elevation until the eighth to thirteenth day following perforation. One of these latter cases had a disruption of the abdominal wound with a partial evisceration five days postoperatively during a quite violent episode of delirium tremens. Five days later (10 days

following the perforation), the patient had a serum amylase of 298 mg. per cent and a serum lipase of 3.5 c.c. These elevations may have been due to the peritonitis which possibly followed the evisceration. Three of these five cases died. Autopsies were performed on two of these patients. Sections from the pancreas were normal in both cases. We were unable to correlate the height of the serum pancreatic enzyme levels with the severity of the symptoms or the prognosis.

Four of our 21 cases had partial small bowel obstruction. In the first of the cases reported above, the one which stimulated our interest in this study, the picture is not clear cut, since generalized acute peritonitis and kidney failure were associated with the obstruction. The other three cases were simple partial small bowel obstruction, two of which responded to Miller-Abbott intubation, while the other had an exploratory laparotomy, during which an internal hernia of the jejunum was reduced and repaired. The pancreas was not inspected at operation. The highest amylase recorded in these three cases was 217 mg. per cent, while the highest lipase was 2.5 c.c. The height of the serum amylase and lipase curve in these three cases was obtained on the fifth to the fourteenth day. There was no correlation between the height of the serum pancreatic enzyme levels and the severity of the patient's symptoms. Two patients were totally asymptomatic with serum lipase levels of 1.5 c.c. and 2.5 c.c.

Eight of the 21 cases had acute peritonitis. The causes of the peritonitis were: two cases of stab wounds of the abdomen without bowel perforation, one hemoperitoneum of unknown etiology, one ruptured urinary bladder, one ruptured appendix, one ulcerative colitis with subacute perforation of the colon, one following evisceration from a postoperative wound disruption, and one peritonitis of unknown etiology. The highest serum amylase recorded in these eight cases was 405 mg. per cent, while the highest serum lipase was 5.2 c.c. The first elevation of the serum lipase and amylase values was five to seven days, on the average, following the onset of the peritonitis. The peak of the curve was reached five to seven days following the first elevation, and levels of both enzymes remained elevated for two to three weeks. In only one of these cases was the pancreas carefully inspected during operation, and that was the case of ulcerative colitis with two walled-off perforations of the colon which had a serum amylase level of 259 mg. per cent and a serum lipase level of 3.1 c.c. 24 hours before operation. The walled-off colonic perforations were in the cecum and splenic flexure. The latter area was adherent to the stomach but not to the pancreas. At operation the pancreas was grossly normal. No biopsy was taken. In this group of cases we were unable to correlate the height of the serum pancreatic enzymes with the severity of the symptoms or the prognosis.

One of the cases of this series was a 13 month old infant admitted because of hematemesis. The child died less than 24 hours after admission. The only serum amylase determination was 388 mg. per cent, and the serum

lipase was 1.9 c.c. The autopsy revealed a diaphragmatic hernia with torsion and strangulation of the stomach. The pancreas was grossly and microscopically normal.

The last three of our 21 cases had elevations of the serum enzymes in association with renal impairment. One of these patients had been subjected to peritoneal lavage for five days before the serum amylase and lipase values were determined. The serum amylase level was 78 mg. per cent and the serum lipase was 2.8 c.c. The blood urea nitrogen at this time was 270 mg. per cent. The generalized subacute peritonitis usually associated with peritoneal lavage possibly influenced the elevated serum lipase value in that case. One patient presented a marked uremia, with a blood urea nitrogen of 210 mg. per cent, while at the same time the serum amylase level was 326 mg. per cent and the serum lipase level was 5.9 c.c. As this patient improved the blood urea nitrogen gradually fell. This fall was paralleled exactly by the serum pancreatic enzyme levels. On the eighteenth hospital day the blood urea nitrogen was 15 mg. per cent, the serum amylase value 170 mg. per cent and the serum lipase value 1.7 c.c. The last of these three cases was a severe transfusion reaction with renal shut down. The blood urea nitrogen rose rapidly, and on the seventh day following the reaction was 162 mg. per cent and on the ninth day was 144 mg. per cent. The serum amylase levels on these two days were within normal limits, but the serum lipase values were 2.2 and 3.0 c.c., respectively.

Discussion

In this series only one case had a serum amylase determination of over 400 mg. per cent, and this was on the twelfth day of peritonitis following a ruptured appendix. Six of the 21 cases had elevations of serum amylase activity above 300 mg. per cent. The majority of elevated determinations were between 200 and 300 mg. per cent.

The highest serum lipase value recorded in this series was 6.2 c.c. This was obtained in a case of a pyloroduodenal ulcer with a subacute perforation into the liver. Six of the 21 cases had elevated serum lipase values above 4.0 c.c., while the majority of the elevations were between 1.5 c.c. and 4.0 c.c.

Special attention was paid to the time of elevation of the serum pancreatic enzymes in relation to the day of the disease. Of the four cases of acute perforated peptic ulcer, two had elevated serum amylase and lipase levels within the first 24 hours following the perforation, while two had elevated studies only after eight to 10 days. In the remaining case, the exact time of perforation could not be determined. Three of the four cases had free anterior perforations of the stomach. The fourth acute perforation was a posterolateral perforation of the duodenal cap. An additional case of subacute perforation of a pyloroduodenal ulcer into the liver was cited. When one speculates concerning the cause of the elevation of the serum pancreatic enzymes in these five cases, the most attractive hypothesis is that

the soiling had produced an inflammation of the posterior peritoneum overlying the pancreas, with possibly some block to the outflow of the external pancreatic enzymes. This is pure speculation; on the two sections taken at autopsy no abnormality of the pancreas was seen. The operative trauma probably did not play any part in these cases. It is of particular interest that in none of these cases did the serum amylase values reach a height such as that frequently seen in acute pancreatitis, namely, 500 mg. per cent and above. It might be reasonable to say that abdominal pain associated with a serum amylase value of under 500 mg. per cent is commensurate with a diagnosis of acute perforation of a peptic ulcer, while an elevation above 500 mg. per cent should make the diagnosis of acute pancreatitis more likely. It would seem from this series that the same generalization cannot be made from the serum lipase values. Certainly a 6.2 c.c. reading is as high as any serum lipase determination we have had with acute pancreatitis. The most important lesson to be learned from these cases is that an elevation of serum pancreatic enzymes can occur in association with an acute perforated peptic ulcer, regardless of the site of the perforation.

In the four cases of partial small bowel obstruction with elevated serum pancreatic enzymes, the height of the determination was first seen six to eight days following obstruction. The serum lipase values showed a higher comparative elevation than did the serum amylase values. The average peak elevation of the serum amylase values was 180 mg. per cent, while the average peak serum lipase value was 2.1 c.c. There is no proved explanation for this elevation of serum pancreatic enzyme values, but it is important to know that such elevations occur in association with partial small bowel obstruction, since it is of differential diagnostic importance in distinguishing between actual mechanical obstruction and the ileus which may be associated with acute pancreatitis.

Acute peritonitis of almost any etiology may give elevated serum pancreatic enzyme values. These elevations were first seen from five to 10 days following the insult, and were equally reflected in both serum pancreatic enzyme values. The values remained elevated for a longer time in this group than in any of the others. One case, a stab wound of the abdomen with partial evisceration but without bowel perforation, had elevated serum pancreatic enzyme values on the sixth hospital day and the serum lipase determination remained elevated for two weeks. The elevations of the serum pancreatic enzymes in association with acute peritonitis do not have the differential diagnostic importance of the preceding two groups. However, it indicates that there is a degree of pancreatic insult associated with some cases of acute peritonitis, and that this insult is reflected in the elevated serum pancreatic enzyme values for comparatively long periods even after the patient has become totally asymptomatic. Just how important this pancreatic insult is to the prognostic evaluation of the case it is difficult to say.

The three cases of uremia showed elevations of the serum pancreatic

enzyme values in association with the elevation of the blood urea nitrogen. In the case diagnosed as an acute exacerbation of chronic glomerulonephritis, there was a complete parallelism of these three laboratory tests. As the patient recovered, all three fell in a straight curve. It would seem that the elevations of the serum pancreatic enzymes in this case were on an impaired excretory basis.

Finally, in none of these 21 cases was it possible to correlate the severity or the prognosis of the disease with the time, degree or duration of elevation of the serum pancreatic enzyme values.

Summary

Twenty-one cases with elevated serum pancreatic enzyme values without primary intrinsic pancreatic disease have been presented. A review of the literature pertinent to these observations has been attempted.

Acknowledgment. The author is indebted to Dr. E. B. Burgoon, of the resident staff, for his stimulating interest in this study, and to Miss D. Merritt Jones and Miss Margaret McCleary for their technical assistance.

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CLINICAL EVALUATION OF AUROTHIOGLYCOLANILIDE (LAURON-ENDO) IN RHEUMATOID ARTHRITIS *

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A gold preparation, characterized by slow absorption after intramuscular injection, has recently been studied in the treatment of rheumatoid arthritis. This preparation, aurothioglycolanilide (Lauron, Endo products), has been the subject of three clinical reports, all of them favorable and all pointing out the lesser incidence of toxicity from this compound as compared with the soluble gold preparations.

In 1944, Stengel [1] treated 30 cases of rheumatoid arthritis with aurothioglycolanilide and found that three cases became completely arrested, 17 showed marked improvement, seven showed moderate improvement and three showed slight to no improvement.

Robinson [2] reported on 55 cases treated with aurothioglycolanilide and stated that 72 per cent of the cases showed a reduction in sedimentation rate, compared with 80 per cent of patients treated with myochrysine.

Rose [3] reported on 91 cases in 1947 and found that 73 per cent had complete or practically complete recovery while under Lauron therapy. Eleven per cent had a partial response. In 22 cases, however, the sedimentation rate rose while under therapy; in this group there was approximately the same percentage claiming and demonstrating improvement as in the entire group.

It is the purpose of this paper to evaluate this drug by comparing a placebo treated control group of rheumatoid arthritis patients with a Lauron-treated group.

Methods

The control group consisted of patients treated either with saline injections, serum injections (rabbit or goat) or antireticulocytotoxic serum ("A.C.S."). We have included "A.C.S." patients since in a previous unpublished study, we found no difference in response to treatment between them and the saline- or serum-treated groups. This control group consisted of the unselected cases of rheumatoid arthritis admitted to the Arthritis Clinic of the Cedars of Lebanon Hospital in 1945 and 1946. They were treated by the same doctors and came from the same social and economic groups as the gold-treated patients. In five cases the same patient served as

* Received for publication April 3, 1950.
From the Arthritis Clinic, Cedars of Lebanon Hospital.

both control and gold-treated patient, since from 1946 to 1947 they received control injections, and in 1947 and 1948 they received gold.

In all cases, the diagnosis of rheumatoid arthritis was obvious and indisputable, as shown by capsular tenderness, location of joints involved, roentgen-ray picture and other classic findings. A number of cases in which there was a question of the diagnosis were dropped from this study.

The 44 control patients were given injections from twice weekly to bi-monthly. The serum injections not infrequently produced mild local and

TABLE I

Lauron-Treated Patients

Name	Age	Sex	Severity Index	Duration of Treatment	Milligrams of Gold	Subjective Improvement	Initial Sed. Rt.	Final Sed. Rt.	Reactions
				months					
G. R.	48	F	3	6	2300	0	44	41	
B. P.	56	F	3	6	2500	0	43	40	
O. K.	41	M	2	6	1600	0	34	30	Skin
H. B.	26	F	2	7	3175	0	29	30	
R. S.	54	F	3	12	5425	0	47	39	
B. B.	45	F	2	9	3200	0	40	43	
M. L.	62	F	3	15	3350	Improved	28	36	Skin
B. S.	62	F	2	9	3450	Improved	21	34	
J. T.	63	F	3	6	1500	0	22	24	
L. S.	40	F	4	9	9500	Improved	34	43	
D. Mc.	55	F	2	18	6825	Improved	43	18	
E. V.	70	F	1	6	2425	Improved	45	19	
E. S.	44	F	3	6	1500	Improved	45	42	
M. W.	52	M	3	7	1525	0	38	38	
G. B.	41	F	2	6	1575	0	43	46	
J. S.	65	M	3	10	2450	Improved	40	35	
S. U.	29	F	3	6	2300	0	43	29	
A. K.	61	F	3	16	2225	0	28	29	
O. S.	51	F	2	6	1425	0	40	34	
F. C.	29	F	3	16	3050	0	33	27	
S. L.	51	F	3	12	4200	Improved	41	45	
I. F.	50	F	2	8	4950	0	41	41	
B. D.	53	F	3	6	3000	Improved	43	38	
A. K.	54	M	2	7	3050	0	37	30	
A. K.	58	F	1	6	3600	Improved	36	42	
N. R.	48	F	3	6	3550	0	46	47	
A. A.	59	M	3	9	4400	0	23	30	
Average	51 yrs.		2.6		3,280 mg.	37% Improved	37mm./hr.	35 mm./hr.	

general reactions. No case is included which was treated for less than six months and followed for less than 12 months, including the period of treatment. The actual average time of treatment is slightly less than a year per patient, and the average period of observation is about two years per patient. The patients were repeatedly examined at bi-weekly to bi-monthly periods, and their statements, as well as any objective changes apparent to the doctor, were recorded.

Sedimentation rates were checked in all cases at the beginning of therapy and at the end, and on occasions during the period of observation. The final

sedimentation rate is not necessarily the last sedimentation rate recorded, but was, rather, that sedimentation rate taken after the completion of therapy showing the maximal improvement. Early in this study a number of rates were taken by the Linzenmeier method, the remainder by the Wintrobe methods. Experimentally, rates were done by both methods on a number of blood specimens, and a table of conversion was worked out so that Linzenmeier results might be compared with Wintrobe figures. It is realized

TABLE II

Control Patients

Name	Age	Sex	Severity Index	Duration of Treatment	Subjective Improvement	Initial Sedimentation Rates	Final Sedimentation Rates
B. J.	38	F	4	1½ years	0	35	37
G. R.	48	F	3	1½ years	Improved	42	44
R. B.	41	F	1	6 months	0	5	5
L. R.	47	F	3	6 months	Improved	37	38
M. R.	37	F	2	1 year	Improved	33	27
B. S.	62	F	2	1 year	Improved	28	18
I. T.	54	F	3	2 years	Improved	45	37
L. S.	40	F	4	1½ years	Improved	45	45
M. E.	48	F	1	6 months	0	20	20
S. S.	57	M	2	1½ years	0	10	12
I. W.	18	F	2	1 year	0	20	20
E. A.	51	F	3	5 months	0	39	39
R. S.	53	F	3	6 months	Improved	49	47
S. L.	25	F	2	1 year	0	42	42
M. B.	32	F	2	9 months	0	15	32
L. M.	35	F	3	1 year	0	44	44
G. G.	50	F	2	9 months	0	20	25
F. C.	29	F	3	1½ years	0	37	37
R. B.	52	F	2	6 months	0	12	22
S. J.	59	M	3	2 years	0	23	22
E. K.	57	F	3	6 months	0	37	37
V. S.	56	F	2	6 months	Improved	29	26
S. C.	52	F	3	6 months	0	26	46
S. L.	51	F	3	1 year	Improved	32	37
G. L.	47	M	4	6 months	Improved	40	44
A. L.	35	F	2	1½ years	Improved	38	45
V. C.	40	F	2	6 months	Improved	45	37
M. S.	54	M	2	1 year	Improved	17	24
A. K.	61	F	3	1 year	0	41	28
R. R.	63	F	2	8 months	0	40	46
O. S.	51	F	2	6 months	0	43	43
V. D.	41	F	3	16 months	Improved	32	29
M. R.	46	F	3	1½ years	Improved	14	30
M. S.	50	F	3	2 years	Improved	36	35
L. B.	37	M	2	16 months	0	26	29
G. B.	41	F	2	1 year	0	38	27
J. G.	56	M	3	1½ years	Improved	33	43
S. U.	29	F	3	6 months	0	42	48
E. R.	38	F	2	7 months	0	50	48
E. H.	36	F	4	3 years	Improved	37	37
G. K.	58	M	2	6 months	0	23	37
F. F.	55	F	3	1½ years	Improved	51	40
J. S.	50	F	3	1½ years	Improved	51	40
B. R.	27	M	2	1 year	Improved	18	18
Average	46 years		2.4		43% Improved	33 mm./hr.	34 mm./hr.

that conversion, in the face of a change in hemoglobin, is likely to be erroneous; consequently, no cases are included in which a significantly changing hemoglobin was present. A slowing of the sedimentation rate of 8 mm. per hour was arbitrarily taken as a significant improvement.

The Lauron group consisted of 28 patients under active treatment for six months or more, with the exception of one case in which treatment had to be stopped at the end of one month because of a skin rash. This case is not included in the evaluation of results. The period of post-treatment observation was at least an additional six months in every reported case. Blood and urine checks were done weekly. The average total dosage was 3,280 mg. of sodium aurothioglycolanilide. A comparison of the characteristics of the gold and control groups is presented in tables 1 and 2.

We found that a change in the degree of motion in an involved joint is a fluctuant matter, partly dependent on the general state of the patient's well being, the time of the day and the weather. Also, the actual degree of swelling in the various joints did not lend itself readily to measurement or classification. Consequently, we used the sedimentation rate exclusively as

TABLE III

Cases	Patients Subjectively Improved	Percentage of Patients Subjectively Improved	Average Change in Sedimentation Rates	Number of Patients Showing 8 mm./hr. Improvement	Percentage of Patients Showing 8 mm./hr. Improvement
Control 44	19	43%	1 mm./hr. faster	6	13.5%
Lauron 27	11	37%	2 mm./hr. slower	3	11%

a yardstick of objective improvement. The subjective improvement is the patient's opinion of the condition of his rheumatism. The severity of the rheumatism was graded by several different examining physicians in each case and the average value recorded. A case graded I is the mildest type of active rheumatoid arthritis recognizable clinically; grade IV is a bedridden febrile patient; the other grades are intermediate. The number of joints involved and the pain, as well as the degree of involvement, were taken into consideration.

RESULTS

There was no essential difference in the results, either subjective or objective, in the Lauron-treated and control groups. In the former, 37 per cent were improved subjectively and 11 per cent showed a slowing sedimentation rate; in the latter, 43 per cent showed subjective improvement and 13 per cent showed a slower sedimentation rate. In our group of 27 Lauron-treated patients, there was apparently no significant benefit from the administration of gold.

Three patients developed skin rashes while receiving gold. These closely resembled seborrheic dermatitis and, as a matter of fact, were erroneously

so diagnosed on the first visit to the dermatologist. In none of the cases were the rashes severe, and all disappeared in less than two months. One of the three developed a rash after one month of therapy and is not included in the tables.

There were no blood or urine abnormalities attributable to the gold.

Comment

The objective of this study was to evaluate the effectiveness of Lauron in rheumatoid arthritis, and, although a definite and negative answer was obtained, several other facts of equal or greater importance came to light during the investigation.

One of these points is the need, in all reports of the therapy of rheumatoid arthritis, for rigid control cases, absolutely parallel to the treated cases. Earlier in our work we had intended using private patients to swell our number of Lauron-treated cases. However, our severity index was lower for this group of private patients than for the clinic group, so that a fair comparison could not be made. It is the impression of several of us (who also work at a county institution in the area) that the severity of the cases seen there is greater than at the Cedars of Lebanon, where the nutritional and financial status of the clinic patients is higher. Certainly our figure of only 13.5 per cent objective improvement is lower than that observed in other clinics.

The explanation for this variation is obvious. The financial and social aspects of the several institutions involved, as well as of private practice, patients seen in a county institution are likely to be sicker and to have further advanced diseases than are those seen at an institution where some patients are allowed to pay part of their costs, as at the Cedars of Lebanon. It is therefore apparent that one must question the validity of any report in which the treated group is not controlled, or in which it is compared with a controlled group handled by a different group of doctors in a different clinic.

The rôle played by psychologic factors in any chronic disabling disease was repeatedly demonstrated in our series.

The percentage of subjective improvement in the controls (43) was much greater than the percentage of improvement in sedimentation rates (13.5). This was largely due to the great longing of the patient to be rid of his disease. It is pathetic as well as enlightening to see the enthusiasm and triumph displayed by the patient over insignificant improvement, such as slightly better flexion of one digit. Most of our patients claimed themselves improved if one joint became better, even though another flared up at the same time. In addition, very often improvement in performance—such as walking, combing the hair, getting into or out of the tub—was parallel to the patient's general feelings of optimism, faith or encouragement, rather than to any changes in the sedimentation rate. We found that, by varying the enthusiasm of our approach and rephrasing our questions, we could in

many instances elicit, in quick succession, responses from the same patient indicating improvement, deterioration or no change. These facts re-emphasize the dangers of depending too heavily on the value of subjective improvement in evaluating therapy in rheumatoid arthritis.

Since many of the reports in the literature on the effects not only of Lauron but also of gold generally and of radiotherapy have committed these errors, their results should not be accepted as final.

Summary

A serum, saline or "A.C.S." treated group of patients with rheumatoid arthritis is compared with a Lauron-treated group.

The group treated with Lauron demonstrated no greater improvement than the control group.

Certain common errors in the evaluation of the effect of therapy on rheumatoid arthritis are pointed out. These include: no control group; a control group treated in a different clinic or by different doctors; mixing of heterogeneous social, intellectual and financial elements in the control or the treated groups.

Subjective improvement is a treacherous yardstick in the evaluation of any therapy in this disease.

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WHAT IS CHRONIC BRUCELLOSIS?*

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"If only the schoolmen had measured instead of classifying,
how much they might have learnt!"
From—Science and the Modern World
Alfred North Whitehead.

Although brucellosis was defined as a human infection toward the close of the Nineteenth Century, subsequent understanding of the illness was confused by attempts at classifying the clinical forms of the disease. Brucellosis does have a variable clinical pattern. For this reason, it is understandable why Hughes,[1] in one of the earliest and best descriptions of the disease, classified brucellosis under four types—the malignant type, the undulatory type, intermittent type, and the irregular and mixed types. This classic description has been modified many times by later investigators. At first, interest in human brucellosis in the United States was desultory, but Alice Evans,[2] working as a bacteriologist in the Dairy Division of the U. S. Bureau of Animal Industry, had made the basic observation that the organism causing abortions in cattle was not the same as the one responsible for a similar disease in goats. Evans [3] also pointed out quite early that cattle with brucellosis were a source of human disease, and subsequently she emphasized that many human cases of brucellosis were being overlooked because of the chronic and insidious nature of the disease.[4-9] Today there are many proponents of the thesis that brucellosis as a chronic disease is being neglected by clinicians. A concept of chronic brucellosis has been summarized recently by Harris.[10] While much has been written and said about the incidence of brucellosis in general, and chronic brucellosis in particular, dependable epidemiologic data are lacking.

The problem of human brucellosis in the United States is enveloped in a wide divergence of opinion and facts concerning the entity of chronic brucellosis. There are those enthusiasts who maintain that chronic brucellosis is a frequent cause of human disability, while on the other hand, there are those skeptics who do not accept the criteria that are used for the diagnosis of chronic brucellosis. Since human brucellosis is a not uncommon disease in some areas in this country, and since there does exist considerable controversy concerning the incidence and the clinical and diagnostic aspects of chronic brucellosis, it is pertinent to review the experience of a clinic in which brucellosis has been under investigation for a number of years.

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 12, 1951.

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The Epidemiology of Human Brucellosis

A comprehensive delineation of the clinical phases of brucellosis is dependent upon certain epidemiologic factors. Such information is particularly helpful in the diagnosis of brucellosis. It cannot be emphasized too strongly that human brucellosis can be caused by any one of three species of brucella: *Brucella melitensis, Brucella suis* and *Brucella abortus.* In general, the clinical picture varies according to the species causing illness with respect to severity, complications and duration. *Br. melitensis* is the most invasive of the three species and frequently causes a severe and prolonged illness. The next most invasive species is *Br. suis,* which causes suppuration and chronic disease. The least invasive species is *Br. abortus.* There are many exceptions to these general statements, but for the most part they apply to the over-all problem of brucellosis. A recent attempt to determine the etiology of human brucellosis in the United States resulted in a survey based on cultural studies which showed that over one-half of the cases were due to *Br. abortus,* about one-third were due to *Br. suis,* and the remainder of the cases were caused by *Br. melitensis.*[11] In Minnesota, over 80 per cent of the cases have been due to *Br. abortus,* with the remaining cases caused by *Br. suis* and *Br. melitensis.*[12] While bacteriologic data are lacking in several areas in the United States, there is dependable evidence which would indicate that as many as three-fourths of all the cases of human brucellosis are due to *Br. abortus.* In other words, brucellosis in this country is primarily a disease caused by *Br. abortus.* In Mexico, parts of Argentina, southern France, and in Italy, brucellosis is caused by *Br. melitensis.* In England and Puerto Rico, *Br. abortus* appears to be the sole cause of human disease. Since the severity of an illness caused by brucella depends to a considerable extent upon the invading species, it is understandable why attention must be focused upon the species causing the disease. This epidemiologic information explains in part many of the conflicting interpretations of the clinical manifestations of the disease that have been presented by physicians in various parts of the world.

Additional epidemiologic information that is of aid to the clinician relates to who acquires brucellosis, and to how the disease is contracted. On the basis of bacteriologically proved cases, it has been shown in Minnesota that approximately three-fourths of all the infections occurred in adult males.[12] Furthermore, about three-fourths of the cases were due to direct contact with infected animals and their environment, while about one-fourth were caused by the consumption of unpasteurized cow's milk. In addition, the disease occurred most frequently among certain occupational groups, such as farmers and meat packing plant employees. It is significant that essentially the same findings have been reported from other endemic areas, such as Iowa [13] and Wisconsin.[14]

Host-Parasite Relationship in Brucellosis

It has been known for many years that brucellosis represents an intracellular form of parasitism in which brucella localize within the phagocytes of the reticuloendothelial system.[15, 16] Subsequent experimental evidence by Goodpasture and his associates [17, 18] indicated that the brucella may actually multiply within the tissue cells. These features of intracellular habitation have been confirmed and extended in our laboratory by Dr. A. I. Braude. It has become apparent that this host-parasite relationship might explain the chronic clinical course and frequent exacerbations occurring in some patients. Recent in vitro experiments in our laboratory have shown that intracellular brucella are protected from the lethal action of antibiotics and combinations of antibiotics such as streptomycin and aureomycin.[19] The implication of these latter observations is that, even with the best available therapy, viable brucella may persist in the tissues for long periods of time.

Diagnostic Criteria for Active Brucellosis

With but few exceptions, brucellosis is a sporadic illness. While the physician may suspect the presence of active brucellosis in a given patient on the basis of historic evidence and as a result of a physical examination, a precise diagnosis is dependent upon information obtained from the laboratory. Reference has already been made to certain epidemiologic data that may be helpful in the establishment of a diagnosis of brucellosis. It is not necessary to detail here the symptomatology and physical findings in brucellosis. This information is not specific for the disease and is described in any standard textbook of medicine. However, certain laboratory procedures and the intradermal test for brucellosis merit discussion.

Intradermal Test for Brucellosis: Since the clinical features of brucellosis are not specific, and since it is extremely difficult to measure the activity of the disease, many clinicians employ the intradermal test to aid them and their patients in a diagnostic dilemma. Several different types of brucella antigens have been used for the skin test, including purified protein, nucleoprotein (brucellergen), and heat killed cells. It is universally agreed that a dermal reaction to brucella antigen or antigens denotes previous invasion of the tissues by brucella. Most physicians are agreed that a positive test does not necessarily signify the presence of active disease. The dermal test has been utilized most frequently in suspected cases of chronic brucellosis, and very often the deciding factor in favor of activity in such a case has been a positive skin test. This clinical practice is widespread in this country, although accumulating scientific evidence is against the procedure. Darley and Gordon,[20] in a careful evaluation of the skin test in suspected cases of chronic brucellosis, concluded that indolent brucellosis was a clinical entity but that the decision in an individual case could not be based upon a positive or negative skin test. It has been observed in Minnesota that around 20

per cent of the adult population react to the intradermal injection of brucella antigen. Under such conditions, the skin test is of no diagnostic help in the evaluation of a suspected case of brucellosis. Dermal hypersensitivity to brucella antigens may persist for many years following the initial infection. The skin test was abandoned several years ago as a diagnostic aid in the clinic at the University of Minnesota Hospitals.

Agglutination Test: It is often stated in the literature and is widely accepted in practice that in chronic brucellosis agglutinins for brucella are frequently absent from the serum and hemocultures are rarely positive. This implies that the final diagnosis of chronic brucellosis rests upon the symptomatology and a demonstration of dermal hypersensitivity. At best, such a conclusion is presumptive and does not seem a sound clinical practice for the elucidation of the problem. Another statement frequently made is that, in chronic brucellosis, agglutinins are often absent but brucella may be cultured from the blood of suspected cases. Again, this statement is not backed up by convincing data.

Over a period of several years the agglutination test has been carefully evaluated in the clinics of the University of Minnesota Hospitals, involving several thousand individuals with and without brucellosis. It is to be recalled that these observations have been made in persons living in an endemic area of brucellosis. As a result of this experience, certain conclusions have been drawn concerning the diagnostic value of the agglutination test. Aside from the actual isolation of brucella from the tissues or blood, the agglutination reaction has been the most reliable diagnostic test. When a reliable antigen is used, and the test is performed under optimal conditions, it is extremely rare to recover organisms from the blood in the absence of agglutinins. In the presence of a bacteremia, over 90 per cent of the patients have had a titer of one to 320 or higher.[12] In an endemic area, a large number of healthy individuals may have a low titer of agglutinins. In one study in this clinic involving 1,627 blood donors, it was observed that agglutinins were demonstrated in the blood of 18.54 per cent.[21] But only 1 to 2 per cent had titers of one to 160 and higher. Therefore, one must be cautious in interpreting the significance of a titer below one to 100. The agglutinin titer in culturally proved cases of brucellosis declines within a year after the onset in those individuals who have recovered, but even in persons who apparently have recovered a high titer of agglutinins may be present for a number of years.

Complement-Fixation Test: Technically, this is a more difficult test to perform than the agglutination test and does not yield any more additional information in doubtful cases.

Opsonocytophagic Test: This is an in vitro measurement of the ability of polymorphonuclear neutrophil leukocytes to phagocyte viable brucella. It is a technically difficult test to perform and is a research tool. It is not a dependable test for diagnostic purposes.

Bacteriologic Studies: Every effort should be made to isolate brucella from suspected cases of brucellosis. A dependable culture medium is tryptose phosphate broth or trypticase soy broth. It is unusual in our experience to isolate brucella from the blood of patients whose illness has extended beyond a year, except in those instances where localizing complications are present. Occasionally the organisms may be cultured from aspirated sternal bone marrow, urine, draining sinuses and biopsied lymph nodes of patients whose illness has endured for more than a year. Brucella have been isolated from approximately one-half the cases in this clinic which have been considered to represent active brucellosis.

The Natural History of Brucellosis

Like many other groups, the clinics at the University of Minnesota Hospitals are confronted daily with patients suspected of having chronic brucellosis or with individuals who have been given this diagnosis and who are receiving therapy. These individuals usually have an ill-defined group of symptoms, which are often compatible with psychoneurosis, neurasthenia or an anxiety state. A low-grade fever approaching 100° may or may not be present. Agglutinins for brucella may be absent, and the presence of low titers may reflect previous therapy with vaccine, or a skin test may have induced such titers. The skin test is usually positive. Blood cultures remain sterile. The vast majority of these patients have had extensive treatment for brucellosis without permanent relief. The question that often plagues the staff is, Do these patients have active disease, or do they represent functional disorders? On the basis of objective data one cannot always determine whether active disease is present. Without much question, many of these patients are emotionally unstable, and do have psychoneuroses. If one concludes that these patients do have active disease, the question arises as to what therapeutic measures should be carried out. Neither therapy with antibiotics nor the administration of brucella antigen appears to be the solution.

It became apparent to our group that one way to aid in the resolution of the problem of chronic brucellosis was to study a number of patients having acute brucellosis and follow them for several years. A review of available information indicated that such studies were very much needed in the United States to clarify many clinical problems related to brucellosis. This study was completed with the aid of Dr. Robert Magoffin, in coöperation with many physicians throughout Minnesota and with the help of the Minnesota State Department of Health. In order to acquire a comprehensive picture of the natural history of brucellosis, it was decided to select only those patients who had not been treated with antibiotics known to be effective in brucellosis. As pointed out elsewhere,[22, 23] the terms "acute" and "chronic" when applied to brucellosis have been interpreted so loosely that this, in turn, has contributed to the confusion surrounding the problem of chronic brucel-

losis. In this study, the terms "acute" and "chronic" were used with reference to the *duration* of illness, without regard to the severity of the disease. *Acute brucellosis* signified cases in which the illness had endured for three months or less. *Subacute brucellosis* indicated an illness of three to 12 months in duration, while chronic brucellosis meant the illness had lasted for one year or longer. We were able to follow 65 patients who had had acute brucellosis. Some of these patients have been seen intermittently for seven to 13 years after their initial examination. The minimal follow-up period was one year, and the average period was four and one-half years. It should be emphasized that most of the patients were hospitalized; we have, therefore, studied a selected group of the more seriously ill patients. Among the 65 patients, there were only 12 females. In other words, approximately 77 per cent of the patients were males, a sex distribution which coincides (77.5 per cent) with a much larger number of culturally proved cases previously reported from Minnesota.[12] A similar proportion of males to females has also been observed in studies carried out in the neighboring states of Iowa and Wisconsin.[24, 14] Recognition of this sex ratio is of considerable help in unraveling the problem of chronic brucellosis, since many uncritical reports on chronic brucellosis are concerned largely with females. The age distribution of the patients revealed that over 80 per cent of the cases occurred in the ages between 20 and 50 years, a distribution which also parallels other studies.[12] Over 70 per cent of the males and half of the females had contracted the disease on farms or in meat packing plants, a feature which reaffirms the fact that brucellosis is primarily an occupational disease, and that direct contact with infected animals and their environment plays a major rôle in acquiring the disease.[12]

The diagnosis of brucellosis was established in 41 of the 65 patients by the isolation of brucella; 38 of the cases were caused by *Br. abortus*, two by *Br. suis* and two by *Br. melitensis*. In the remaining 25 cases, epidemiologic data, the clinical features, hematologic information and positive agglutination tests for brucella established the diagnosis. The minimal titer of agglutinins was one to 80, and this occurred in only a few of the patients, over 90 per cent of the patients having a titer of one to 160 or higher.

One of the most difficult features of this study was to quantitate the total duration of illness. There were no fatalities. The duration of illness was finally based on two main criteria. First, subjective data were utilized to determine when the illness in each patient had subsided. Regardless of the results of the physical examination or laboratory tests, a patient was not considered well if he still complained of symptoms. Second, the duration of the illness was based upon more objective evidence, such as physical abnormalities and the results of serologic and bacteriologic studies.

A division of the cases into acute, subacute and chronic brucellosis on the basis of the foregoing criteria revealed that 16 per cent of the 65 cases had only *acute brucellosis*. They recovered completely within three months,

and remained well for from one to seven years. Thirty-nine per cent of the 65 cases had *subacute brucellosis;* they complained of symptoms for from three to 12 months before complete recovery ensued. Continued illness was frequently associated with a persistent bacteremia, or with several relapses, but in many instances there was a protracted period of convalescence without objective evidence of the presence of active disease. In this entire group of subacute cases there was only one patient with a demonstrable complication as a cause for protracted illness, and that patient had meningoencephalitis. Forty-six per cent of the 65 cases had *chronic brucellosis;* their ill health persisted beyond one year. These may be divided into three

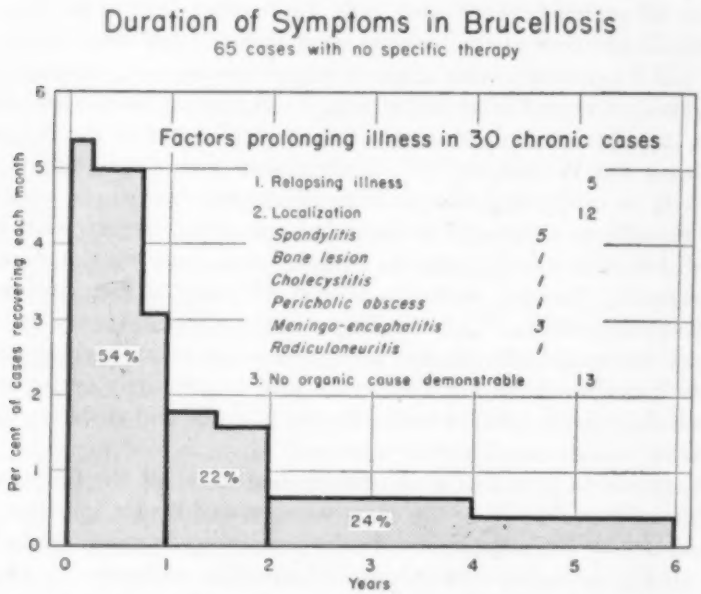

FIG. 1. Illustrating the duration of symptoms, with particular reference to the 30 cases having an illness which lasted more than a year.

groups in seeking the reasons for the protracted illness (figure 1). There were five individuals in the first group who had a relapsing type of illness without evidence of localizing disease, but who had clinical and laboratory evidence of continued infection. All of these patients eventually recovered and have remained well for from one to three years. The second group of chronic cases included 12 individuals who had evidence of a localizing complication, often associated with several relapses. While it was relatively easy to understand why the foregoing two groups of patients had chronic illness, it was difficult in the third group of 13 patients (or 20 per cent of all the cases), who demonstrated no objective evidence of active disease but still complained of ill health. It is patients such as these that make chronic

TABLE I

An Analysis of 30 Cases with Chronic Brucellosis

I. Patients with Subjective and Objective Evidence of Disease but with No Localizing Lesions

No. of Patient, Age and Sex	Occupation	Bacteriologic and Serologic Data at Onset of Illness	Complications	Last Available Titer of Agglutinins	Total Duration of Illness	Factors Prolonging Illness	Final Outcome
1. 36 Male	Machinist	*Br. abortus* from blood. Aggls. 1:1280	Sinusitis	±1:80	15 months	Persistent bacteremia. No specific therapy	Complete recovery. Followed 5 years
2. 11 Female	Student	*Br. abortus* from blood. Aggls. 1:320	None	0	12 months	Persistent bacteremia. No response to streptomycin	Complete recovery. Followed 3 years
3. 33 Male	Laborer in meat packing plant	Aggls. 1:160	None	1:160	3 years	Treated with vaccine by his physician. Possible reinfection while back at work with hog casings	Complete recovery. Followed 3½ years
4. 20 Male	Butcher in meat packing plant	Aggls. 1:1280	None	1:40	2 years	No specific therapy, except rest and sulfonamide	Complete recovery. Followed 3½ years
5. 33 Male	Laborer in meat packing plant	*Br. suis* from blood. Aggls. 1:1280	None	1:320	2½ years	No specific therapy, except rest and sulfonamide. Alcoholism. Possible reinfection while back at work with hog casings	Complete recovery. Followed 4 years and 7 months

TABLE I—*Continued*

II. Patients with Subjective and Objective Evidence of Disease with Localizing Lesions

No. of Patient, Age and Sex	Occupation	Bacteriologic and Serologic Data at Onset of Illness	Complications	Last Available Titer of Agglutinins	Total Duration of Illness	Factors Prolonging Illness	Final Outcome
6. 43 Male	Laborer in meat packing plant	*Br. suis* from pericholecystic abscess. Aggls. 1:400	Osteomyelitis, pericholecystic and hepatic abscesses	±1:40	11 years	No specific therapy. Osteomyelitis drained surgically. Pericholecystic and hepatic abscesses drained surgically. Alcoholism. Morphine addiction. Attempted suicide	Complete recovery. Followed 13½ years
7. 17 Male	Farm boy	*Br. abortus* from cerebrospinal fluid. Aggls. 1:640	Chronic encephalomeningitis	1:320	4 years	No specific therapy, except sulfonamides which controlled infection. Had chronic infection of meninges	Complete recovery with total deafness. Followed 5 years
8. 66 Female	Housewife	*Br. abortus* from blood. Aggls. 1:640	Spondylitis	1:640	1 to 5 years	No specific therapy, except sulfonamides. Spondylitis and progressive cirrhosis of liver	Died of cirrhosis of liver. Followed 5 years
9. 35 Male	Ranchman	*Br. abortus* from cerebrospinal fluid. Aggls. 1:640	Chronic encephalomeningitis	1:640	5 years	Chronic infection of meninges	Complete recovery. Followed 4 years
10. 64 Male	Well driller	*Br. abortus* from blood. Aggls. 1:640	Spondylitis	0	1 year	Spondylitis. No specific therapy	Complete recovery. Followed 10 years
11. 25 Male	Clerk	*Br. abortus* from blood. Aggls. 1:2560	Spondylitis	1:40	2 years	Spondylitis. No specific therapy	Complete recovery. Followed 10 years
12. 41 Male	Farmer	*Br. abortus* from blood. Aggls. 1:640	Chronic cholecystitis	0	1 year	Chronic cholecystitis	Complete recovery. Cholecystectomy. Followed 6½ years
13. 57 Female	Housewife	*Br. abortus* from blood. Aggls. 1:5120	Neuritis left arm	0	20 months	Severe neuritis	Complete recovery. Followed 3 years
14. 12 Male	Farm boy	*Br. abortus* from blood and from left hip joint. Aggls. 1:640	Suppurative arthritis	1:80	1 year	Suppurative arthritis	Complete recovery. Followed 2½ years
15. 21 Male	Farmer	Aggls. 1:320	Spondylitis with pleural effusion. Cultural studies for *M. tbc.* neg. in sanatorium	0	2½ years	Spondylitis. No specific therapy	Complete recovery. Followed 8 years
16. 37 Male	Farmer	*Br. abortus* from blood. Aggls. 1:640	Spondylitis		13 months	Spondylitis. No specific therapy	Complete recovery. Followed 9 years
17. 56 Female	Farmwife	*Br. abortus* from blood. Aggls. 1:1280	Spondylitis with paravertebral abscess. In tbc. sanatorium for tbc. of spine	±1:160	3 years	Spondylitis	Recovery. Residual of fatigue, backache and nervousness. Followed for 2 years

TABLE I—*Continued*

TABLE I—*Continued*

III. Patients with Subjective Symptoms but without Objective Evidence of Disease

No. of Patient, Age and Sex	Occupation	Bacteriologic and Serologic Data at Onset of Illness	Complications	Last Available Titer of Agglutinins	Total Duration of Illness	Factors Prolonging Illness	Final Outcome
18. 38 Male	Laborer in meat packing plant	Aggls. 1:640		1:160	2 years	Psychoneurosis and alcoholism. Discharged from military service—prior to infection—because of "nervousness"	At work. Followed 4 years
19. 21 Male	Laborer in meat packing plant	Aggls. 1:80		1:40	3 years	After psychiatric consultation, diagnosis of psychoneurosis	At work. Followed 4 years
20. 37 Male	Laborer in meat packing plant	*Br. suis* from blood. Aggls. 1:1280		1:640	1 year	Alcoholism. Complete psychiatric study—"psychopathic personality"	At work. Followed 7 years
21. 39 Male	Cattle buyer	Aggls. 1:320		1:160 (received vaccine)	3 years	Litigation over illness. Treatment with vaccine	Recovery. Followed 2 years
22. 45 Male	Laborer in meat packing plant	Aggls. 1:160		1:160 (received vaccine)	3 years	Treatment with vaccine. Psychopathic personality. Very moody	Recovery. Followed 3 years
23. 52 Male	Herdsman (cattle)	Aggls. 1:320	Radiculitis	1:320 (received vaccine)	3 years	Compensation under Workmen's Compensation Law	Recovery. Followed 3 years
24. 29 Male	Farmer	*Br. abortus* from blood. Aggls. 1:2560			20 months	Probably residuals of infection	Still has symptoms after 3½ years
25. 32 Male	Laborer in meat packing plant	*Br. abortus* from blood. Aggls. 1:640		1:160	2 years	Probably residuals of infection. ? of reinfection	Still has complaints. Followed 3 years
26. 35 Female	Farmwife	*Br. abortus* from blood. Aggls. 1:1280		0	6 years	Severe psychoneurosis. Under psychiatric care prior to infection	Still has complaints. Followed 6 years
27. 31 Male	Laborer in meat packing plant	Aggls. 1:160		1:320 (received vaccine)	4 years	Discharged from military service prior to infection because of "inadaptability." Psychoneurosis. Obsessed with idea that "positive" serology means disease	Still has complaints. Followed 3 years
28. 36 Male	Farmer	*Br. abortus* from blood. Aggls. 1:1280		1:40	4 years	Psychoneurosis. Possibly residuals from active infection. Very dependent upon wife	Complete recovery. Followed 4 years
29. 29 Male	Domestic work on farm	*Br. abortus* from blood. Aggls. 1:640		±1:160	4 years	Possibly residuals from infection	Still has complaints. Followed 4 years
30. 36 Male	Laborer in meat packing plant	Aggls. 1:1280		±1:160	2 years	Possibly residuals from infection	Complete recovery. Followed 2 years 5 months

brucellosis such a perplexing problem; a careful study of these patients has shed some light on the causes for continued ill health.

The pertinent clinical and laboratory data of the 30 patients with chronic brucellosis are summarized in table 1. It is significant that there were only five females. The first group included the five patients with objective evidence of active disease but no localizing lesions. Two of the patients worked in meat packing plants, and reinfection was brought forth as a possible cause of persistent illness. The problem of reinfection or relapse as a factor in chronic ill health will be commented upon subsequently. The second group involved 12 patients who had chronic disease with localizing lesions. The most frequently encountered lesions involved bones. There were six cases of spondylitis, one of osteomyelitis and one of suppurative arthritis. The brucella lesions of the spine resemble tuberculosis, but complete recovery over a relatively short period of time ensued in the present cases. It is of interest that this recovery took place in four of the five patients without the aid of the antibiotics now being employed in the treatment of brucellosis. There were three patients with chronic brucellosis who had involvement of the nervous system. Two of these patients had chronic encephalomeningitis, and *Br. abortus* was recovered periodically from the cerebrospinal fluid over a long period of time. These two patients (cases 7 and 9) were ill for four and five years, respectively, and their clinical courses, which have been detailed elsewhere,[25] emphasize that brucellosis is a cause of chronic meningitis. Both of these patients eventually recovered after receiving aureomycin. A third patient (case 13) had a severe neuritis of the arm from which she recovered. The most remarkable example of chronic brucellosis in this series (case 6) had osteomyelitis as a demonstrable localizing lesion. Although this complication was readily controlled, he continued in a state of ill health, becoming quite unstable emotionally. He became an alcoholic and addicted to morphine. Although he had only a low-grade fever and inconstant distress in the right upper quadrant, an exploratory operation revealed a pericholecystic abscess with hepatic abscesses due to *Br. suis*. He recovered from this infection, and then in a period of depression attempted suicide. When seen recently, he apparently had recovered completely. One patient (case 66) had a progressive cirrhosis of the liver from which she died. During the acute phase of her illness, hepatic granulomas had been demonstrated by means of a biopsy.[26] A subsequent hepatic biopsy revealed early cirrhosis of the liver. Brucellosis may have played an important rôle in the genesis of this fatal case of cirrhosis. Not included in this series of complications of brucellosis were three fatal cases of subacute bacterial endocarditis due to *Br. abortus*.[27, 28] These cases were not included because death took place within a year.

It is not difficult to explain the reasons for chronic illness in the foregoing 17 cases, but the problem becomes more complex in the third group of 13 patients, who had subjective complaints of ill health but no reliable objective

evidence of active disease. These patients were studied quite thoroughly and many of them had the benefit of psychiatric consultation. Only one of these patients (case 22) had had previous evidence of a localizing complication, and that was a radiculitis. One of the outstanding features of this group was that over half (cases 17, 18, 19, 21, 25, 26 and 27) were so maladjusted emotionally that diagnoses of severe psychoneurosis or psychopathic personality were made. Further evidence of emotional instability was manifested by alcoholism (cases 17 and 19), and a discharge from military service prior to the onset of infection because of "nervousness" or "failure to adjust" (cases 17 and 26). Some of the individuals had had clear-cut

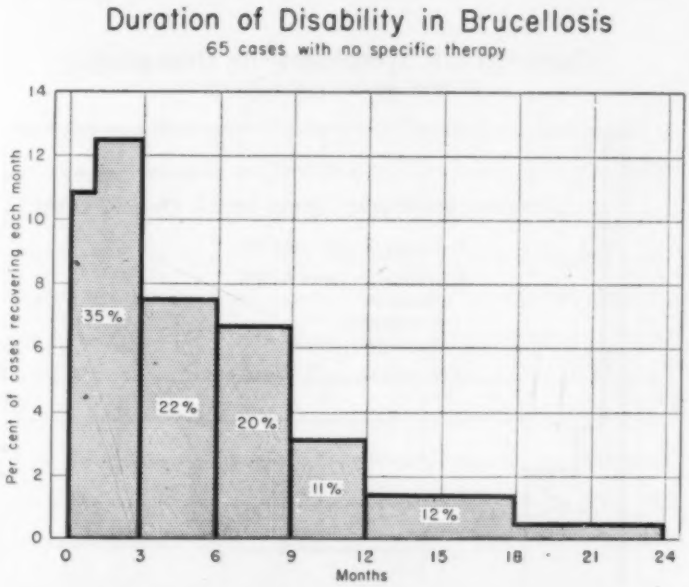

FIG. 2. Illustrating the duration of disability, with particular reference to eight patients or 12 per cent of all the cases who were unable to return to work at the end of one year of illness. Compare this disability with figure 1, showing duration of symptoms.

emotional problems prior to the onset of brucellosis, while in others the disease appeared to provoke emotional instability. It became apparent in this study that a chronic state of ill health was not synonymous with active infection, and that the proper therapeutic approach to a psychiatric problem was not the use of vaccines or antibiotics. Some industries, particularly meat packing plants, compensate financially those employees who acquire brucellosis, and the latter receive this compensation for varying periods of time. To determine when an individual is ready to go back to work after he has had brucellosis is not easy, particularly when objective evidence of active disease is lacking. It became evident in at least two individuals (cases 20 and 22) that the state of their health was intimately related to the outcome

of claims for compensation. Finally, there were those individuals (cases 23, 24, 28 and 29) who had no objective evidence of active infection but who complained of ill health. They were stable persons as far as could be determined, but they felt weak and tired easily. They just did not feel so well as they had prior to their illness. It is difficult to explain the cause of continued ill health in these people.

In the preceding discussion, the duration of ill health in brucellosis has been analyzed on the basis of subjective data. Another approach to the duration of illness was to determine the period of disability for each case. A person was considered disabled if he could not carry out the daily routine he performed before he became ill. There is a marked difference between

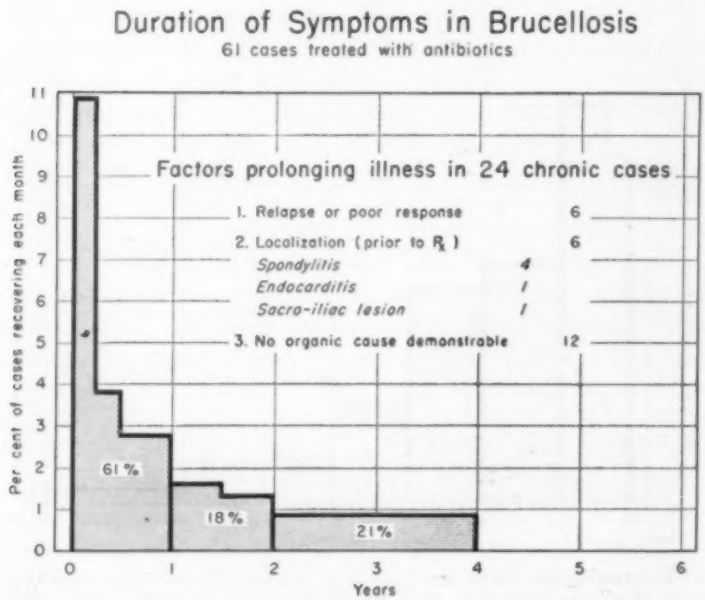

FIG. 3. Illustrating duration of symptoms in 61 patients treated with streptomycin and sulfadiazine, or aureomycin, or chloramphenicol. Compare this figure with the untreated cases in figure 1.

the duration of illness based upon the patient's complaints as compared with the period of disability. This is illustrated by comparing figure 1 with figure 2. While 30 of the 65 cases, or 46 per cent, complained of symptoms beyond one year, only eight cases, or 12 per cent, were disabled beyond that period. In fact, 37 of the cases, or 57 per cent, were able to return to their usual routine at the end of six months, and 77 per cent at the end of nine months. Factors responsible for prolonging the period of disability include a relapsing illness and the presence of localizing complications. In addition, there were a few individuals who could not endure the day's work although no organic cause for their disability could be found.

The Influence of Antibiotic Therapy on the Course of Brucellosis

It is not the purpose of this report to detail the results of therapy with antibiotics. A follow-up study of patients with brucellosis treated with antibiotics will be presented elsewhere.[29] However, a brief reference will be made to a follow-up study of 61 patients who received treatment with one or more antibiotics considered to be effective in this disease. These 61 treated cases have been compared with the 65 untreated cases. It must be pointed out that this analysis is weighted against the advantages of therapy, since many patients had been ill for several months before treatment was instituted. The conclusions are based upon the duration of illness since the onset of symptoms. The treated patients were followed after therapy

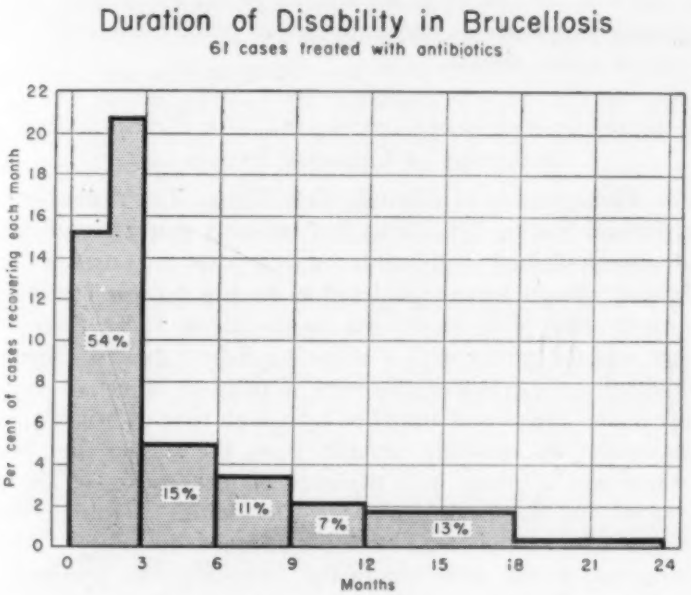

Fig. 4. Illustrating duration of disability in patients receiving antibiotics. Compare this figure with untreated cases in figure 2.

for a minimum of six months and for an average of 2.1 years. Brucella were isolated from 40 of the 61 cases, and included 36 caused by *Br. abortus*, three due to *Br. melitensis* and one due to *Br. suis*. The duration of symptoms in the treated group may be compared with the untreated groups by referring to figures 1 and 3. Although the number of patients in the two groups is almost the same, the outstanding difference is that in the treated group twice the number of patients had fully recovered within the first three months of illness; a total of 37 of the 61 cases, or 61 per cent, had recovered within a year. But there still were a significant number of chronic cases whose illness extended beyond one year. This group comprised 24 cases,

or 39 per cent, and is to be compared with the 30 cases, or 46 per cent, in the untreated group of chronic cases. But of considerable significance is the fact that 12, or one-half, of the 24 chronic cases in the treated groups complained of symptoms for which no organic cause could be demonstrated. This is to be compared with 13 of the 30 cases in the untreated group. Essentially the same number of patients complained of ill health without objective evidence of disease one year after the onset, whether or not they had been treated with antibiotics.

Of additional importance was a comparison of the total number of patients in the treated and untreated groups who were disabled one year after the onset of the illness. There were eight cases, or 13 per cent, in the treated group, and eight cases, or 12 per cent, in the untreated group. (Compare figures 2 and 4.) Disability in the treated group was due to recurring illness, localizing complications and a prolonged postconvalescent period without evidence of active disease.

Some Concluding Remarks Concerning the Pathogenesis and the Diagnosis of Chronic Brucellosis

A. *The Pathogenesis of Chronic Brucellosis:* This follow-up study of over 100 patients having brucellosis has revealed that a significant number of individuals complained of ill health one year after the onset of their illness. Many of these patients were considered as having chronic brucellosis. The basis for their state of ill health can be discussed under three categories. First, there was the group with a relapsing, febrile type of illness. There was no doubt that these individuals were ill from an objective point of view. The nature of the illness was amplified by a high titer of brucella agglutinins and, occasionally, by isolating brucella from the tissues and body fluids. Second, there was a group with evidence of localization of the disease in various organs and tissues of the body. In addition, serologic and bacteriologic studies defined the cause of the continued disability. Third, while little controversy would arise out of the foregoing two groups of patients with chronic brucellosis, the problem of chronic brucellosis centers upon those patients who complain of poor health but in whom objective evidence of active disease cannot be demonstrated. This group comprised about 20 per cent of all of the patients with brucellosis, including those who had received treatment with antibiotics. With almost monotonous regularity they complained of weakness, vague aches and pains, easy fatigability, nervousness and mental depression. With few exceptions, the titer of brucella agglutinins had declined and cultures remained sterile.

If the basic cause for the continued state of ill health in this third group of patients could be determined, the diagnostic problem of chronic brucellosis would be largely resolved. There appear to be three possible explanations for the complaints of this group. First, the symptoms are due to a continued active infection by brucella. While many efforts have been made

to defend this thesis, precise objective data are lacking. The problem cannot be resolved by the results of intradermal brucella tests. Second, the complaints expressed by this group of patients are not specific, and the symptoms fit in with the definition of the functionally disturbed psychoneurotic or neurasthenic patient. In the present study, the majority of the patients having prolonged illness without objective evidence of disease were emotionally unstable individuals. It may be postulated that these persons are suffering from the residuals of brucellosis, and that active disease is not present. As pointed out elsewhere,[25, 30] acute brucellosis does have an impact upon the nervous system, including the autonomic nervous system, and this impact may be reflected in a reaction pattern that persists long after the infection has subsided. Our own observations indicate that patients bordering on a personality disorder or emotional disturbance may be tipped over into a functional state of chronic ill health by an attack of acute brucellosis. Furthermore, individuals with functional complaints or personality difficulties may have an exaggeration of these manifestations following acute brucellosis. Third, Apter and his associates [31] have studied with psychometric tests a small group of patients having chronic brucellosis, and have suggested that the behavior patterns may be due to organic damage to the cerebral cortex. This possibility should be explored further.

B. *The Diagnosis of Chronic Brucellosis:* Studies in our clinic on the epidemiology and the natural history of brucellosis have demonstrated that certain basic requirements are necessary for a precise diagnosis of brucellosis, and these include: (1) history of exposure to the disease; (2) objective as well as subjective evidence of illness; (3) the presence of brucella agglutinins, especially in a titer of one to 100 and above; (4) isolation of brucella from the tissues or body fluids. This often clinches the diagnosis, although the first three criteria may establish it with reasonable accuracy.

One is on very uncertain ground if the diagnosis is based upon: (1) subjective complaints only; (2) a positive intradermal test with brucella antigen; (3) absent, or low titer of brucella agglutinins.

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THE IMPORTANCE OF THE CERVICAL SPINE TO THE INTERNIST *

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Aside from the commonly recognized spondylitis or hypertrophic arthritis of the spine, including the cervical portion, there are two interesting syndromes which are frequently overlooked and misdiagnosed when the physician is not constantly cognizant of the possibility of their presence. The first of these is a lateral rupture of an intervertebral disc of the lower cervical spine producing shoulder, arm and upper anterior chest pain simulating angina pectoris. The second is headache associated with a pathologic process, of as yet unknown etiology, in the upper portion of the cervical spine. Both of these syndromes probably have a traumatic etiology but, as the trauma may be relatively minor and the symptoms quite delayed in onset, the patient seldom consults an orthopedist or neurosurgeon but turns first to the general practitioner or internist for the interpretation of his difficulties.

Syndrome of Lateral Rupture of a Lower Cervical Disc

That localized arthritis of the lower cervical spine was a cause of arm, shoulder and anterior chest pain was recognized by several authors in the 1930's, Nachlas,[1] Hanflig [2] and Reid.[3] In 1932 Keyes and Compere [4] pointed out that destruction of or injury to the intervertebral disc was a cause of localized arthritis of the spine, and their conclusions were sustained by Oppenheimer.[5] For many years, midline rupture and protrusion of a cervical disc producing signs of cord compression have been reported, but before 1940 there were only a few isolated reports of lateral rupture producing radicular signs. Spurling and Scoville [6] gave an excellent description of the syndrome in 1944, and numerous other authors have added their descriptions of the symptoms, findings and treatment of a lateral rupture of a lower cervical disc. Semmes and Murphey [7] in 1943 described four cases with precordial pain caused by lateral rupture of the sixth cervical disc. Josey and Murphey [8] in 1946 reported on seven similar cases producing precordial pain simulating angina pectoris. Three of their cases underwent surgical removal of the herniated nucleus pulposus, with relief of symptoms. Practically all of the dissertations on rupture of the lower cervical discs have been written by neurosurgeons. These writers have naturally seen only the more severe cases. There are many other cases, of less severe degree, whose symptoms go unrecognized or are diagnosed as arthritis, rheumatism, neuritis, psychoneurosis or even angina pectoris. With proper recognition and guidance, many of these cases can receive satisfactory relief and reassurance, or be directed into the proper hands for surgical relief.

* Received for publication March 24, 1950.

The symptoms of lateral rupture of a lower cervical disc vary considerably in extent, severity and distribution. A history of recent or remote trauma is frequently obtained, but it should be kept in mind that even in some severe cases no noteworthy trauma can be recalled by the patient. In all cases, mild or severe, there are a few significant facts. The classic symptoms are neck pain and stiffness, shoulder, suprascapular and arm pain, and numbness of certain fingers, depending on the intervertebral joint involved and the particular nerve root impinged. The pain is usually relatively constant, with exacerbations dependent on position and movement and with coughing and sneezing producing sharp paroxysms. Numbness of one or more fingers, depending on the dermatome involved, will frequently designate the particular offending disc. There may be loss of biceps or triceps reflexes and even atrophy of the muscles of the shoulder girdle or upper portion of the arm. There usually is limitation of motion of the neck due to pain, and a blow on the head with neck rotated and flexed toward the side of the lesion may produce exacerbation of the arm pain. Pressure with the examiner's thumb over the brachial plexus on the involved side produces radiating pain and paresthesia into the arm and one or more fingers. Hypesthesia to pinprick over one or more fingers may be present. Roentgenogram of the cervical spine usually shows a loss of the normal curvature, a reversal of the curvature above the level of the ruptured disc, diminution of the intervertebral space, and evidence of localized arthritis or even partial obliteration of the intervertebral foramen. However, many cases fail to present symptoms of such degree and physical findings may be quite meager. Shoulder and upper arm pain may be present only with certain positions of the neck or after exercise, and may be transient and associated with only a few of the classic physical findings.

In the differential diagnosis, several other conditions should be considered. Subdeltoid bursitis causes shoulder pain which radiates to the upper arm. Localized pain, limitation of motion of the shoulder, the absence of radicular distribution of pain and numbness, and the differences in the roentgen-ray findings should serve to separate these two entities. Localized arthritis of one shoulder usually has a definite traumatic etiology, and definite limitation of motion of the shoulder and roentgen-ray findings should easily separate arthritis of the shoulder from ruptured cervical disc. The syndrome of the cervical rib and the scalenus anticus syndrome may produce arm pain and numbness. How real these conditions are and how frequently they have been confused in the past with a ruptured cervical disc are moot questions. Certainly some descriptions of these syndromes are quite similar, but with increasing knowledge of the nature of lateral rupture of a cervical disc we hear less and less of the scalenus anticus syndrome, and it may well be that these two syndromes have been confused in the past.

For illustrative purposes, four cases of ruptured lower cervical disc are reported briefly:

Case Reports

Case 1. A male lawyer, age 40, was first seen September 22, 1948. He had first noted sharp pains in the right side of his neck and right shoulder when he turned his head sharply in July, 1948. He then developed an aching pain in this arm which was almost constant, worse on arising in the morning and sometimes even bothering him at night. There was no pain or numbness below the upper arm. No history of injury to head or neck could be recalled. Complete physical examination was negative except for limitation of motion of the neck on flexion and right lateral rotation, and the production of radiating pain to the level of the elbow on pressure

Fig. 1. Lateral roentgenogram of normal cervical spine, demonstrating the smooth lordotic curvature.

over the right brachial plexus. Routine urine and blood examinations were normal. Lateral roentgenogram of the cervical spine showed a loss of the normal lordotic curvature, with a poker-type spine above C6. Because of the mild degree of his symptoms, he was advised to do nothing other than to take aspirin as necessary for relief. He was reëxamined on September 1, 1949. There had been very little change in his symptoms, and he had become so accustomed to them that he paid them little attention and took aspirin only on rare occasions.

Case 2. A male contractor, age 32, was first seen October 3, 1946. On September 4, 1945, he had dived into the ocean from a boat, landed on his back and

"snapped his neck." There was little pain at that time, but two weeks later, while bathing in the surf, a companion pushed his neck sharply forward. There was immediate sharp pain in the posterior part of his neck, and he suffered with pain and stiffness in that region for about three weeks. Pain in the right shoulder and upper arm developed in October, 1945, and was associated with numbness in the fourth and fifth fingers on that side. These symptoms continued, and the pain was increased markedly by coughing and sneezing. He found that if he lay supine with a pillow under his shoulders he obtained relief. Complete physical examination revealed nothing significant except that motion of the neck to the right lateral flexed position,

FIG. 2. Lateral cervical spine roentgenogram, case 1, showing loss of normal curvature in upper portion, C1–C5.

pressure on the right brachial plexus and a blow on the head caused radiation of pain from the right shoulder to the lower portion of the right arm. There was no diminution of reflexes or change in sensation to pinprick in that extremity. Lateral roentgenogram of the cervical spine showed straightening of C1 to C6. He was advised to use a pillow under the shoulders at night, wear a leather cervical collar, use head traction and take aspirin as necessary. These measures brought a modicum of relief after many months, and when interviewed September 27, 1949, he stated that he was leading a normal life, with a moderate amount of discomfort, and had discarded the use of any traction or support to the head or neck. He still had some limitation of motion of the neck and radiating pain on pressure over the right brachial

plexus. With head flexed and rotated to the right, a blow on top of the head caused sharp pain down the right arm to the fourth and fifth fingers with increased paresthesias in the fingers. The biceps and triceps reflexes were normal. There was slight but definite hypesthesia to pinprick over the fourth and fifth fingers.

Case 3. A 33 year old housewife was first examined on April 20, 1949. She had first noted mild pain in the neck and right shoulder in July, 1948. No history of any significant trauma could be elicited. The neck pain never became severe, but within a few weeks the pain about the right shoulder region became quite intense and

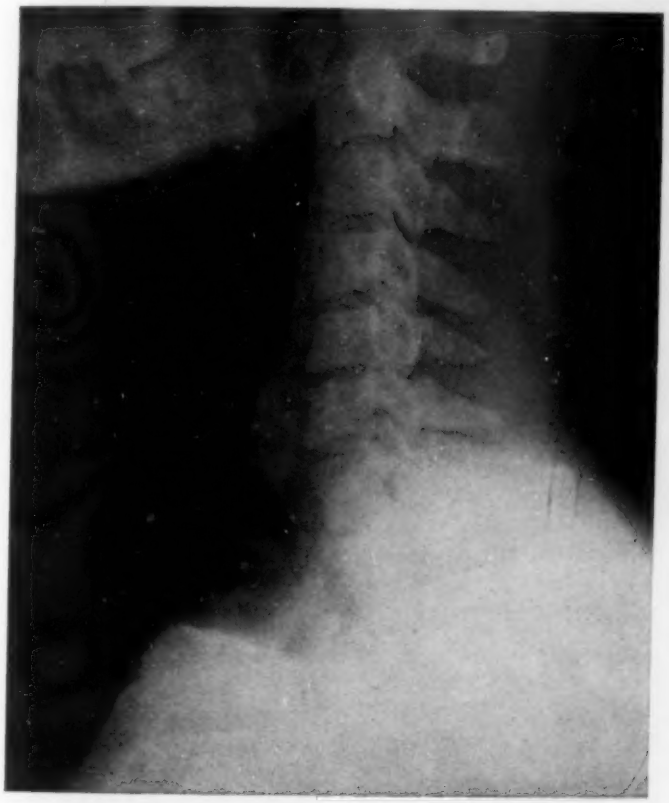

FIG. 3. Lateral cervical spine roentgenogram, case 2. Straightening of alignment of vertebral bodies C1–C6.

radiated into the upper arm. There was associated numbness and tingling of the thumb and forefinger of the right hand. Certain positions of the head seemingly increased her pain; she could not lie comfortably on a pillow and lost sleep. Exertion caused increase in pain and she suffered more after household duties. There had been no noticeable coughing or sneezing, and she had no increased pain on straining at stool. Her symptoms were almost constant, with variable exacerbations. She sought relief from several physicians without avail. Because of the amount of pain suffered, she at times became somewhat emotionally upset and was thought to be "nervous." Tilting of the chin toward the right shoulder and pressure over the

right brachial plexus caused increased arm pain. The right biceps reflex was somewhat diminished. There was slight but definite hypesthesia over the right thumb and index finger. Head halter traction and a cervical collar were used for several months. Although it was thought for a while that she received some benefit, insufficient relief was obtained. A pantopaque myelogram on May 4, 1949, showed a defect between C5 and C6, and operation was advised. This was performed by Dr. Earl Walker, of Baltimore, who found and removed a protrusion of the disc between C5 and C6 on August 17, 1949. When last interviewed on September 20, 1949, the

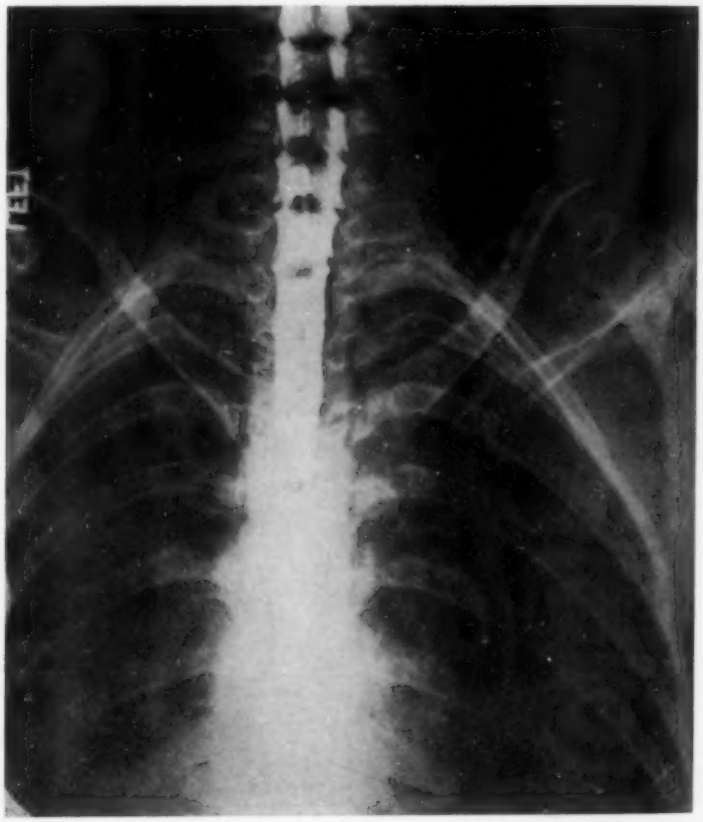

FIG. 4. Roentgen-ray pantopaque myelogram, case 3, demonstrating defect between C5 and C6 on right.

patient was asymptomatic except for a slight tingling sensation of the right thumb and index finger. The right biceps reflex was still slightly diminished, and there was slight hypesthesia of the right thumb and index finger.

Case 4. A 40 year old unmarried woman first noted the onset of transitory pain just to the left of the sternum at the insertion of the fifth rib in January, 1945. Six months later she developed severe precordial pain while in bed at night. There was radiation to the neck, left shoulder and ulnar side of the left arm which lasted approximately half an hour. These attacks were repeated over the period of the next four days and occurred both at rest and on exertion and finally became constant

before she was admitted to the hospital on July 11, 1945. On close questioning she admitted to previous attacks of stiffness in the neck and some numbness in the left index finger. Physical, roentgenographic and electrocardiographic examinations of the heart were normal. Blood pressure was 106 mm. Hg systolic and 66 mm. diastolic. Pressure over the left anterior lateral aspect of the neck at the level of the sixth cervical body produced pain over the precordium and down the left arm to the ulnar side of the left hand. Lateral roentgenogram of the cervical spine showed a loss of the normal curvature, with a reversal at the level of the sixth body. Head halter traction failed to produce relief and she was operated upon by Dr. Francis

FIG. 5. Lateral cervical spine roentgenogram, case 4, demonstrating the loss of normal curvature with a forward angulation in the lower portion. There is a slight lordotic curvature in the upper portion.

Murphey on July 17, 1945. A nodular mass of herniated disc material was found compressing the seventh nerve root on the left. This mass was excised and within a short period of time she became asymptomatic.

SYNDROME OF HEADACHE ASSOCIATED WITH UPPER CERVICAL SPINE PATHOLOGY

This syndrome is more nebulous than that of lateral rupture of the lower cervical disc and lacks the operative or pathologic proofs of the latter. While the author was working with Dr. Francis Murphey and Dr. Samuel Little during the recent war we noted a group of individuals whose com-

plaint was headache and whose lateral cervical spine roentgenograms showed a loss of the normal lordotic curvature.

The loss of the normal curvature of the cervical portion of the spine was investigated and reported on by Hadley [9] in 1944 and Davis [10] in 1945, both of whom stated that the condition was always traumatic in origin. The straightening of the cervical spine has also been noted by some authors (Semmes and Murphey [7] and Josey and Murphey [8]) reporting on lateral ruptures of the lower cervical disc.

Pathologic changes in the cervical region have been assigned for many years a cause of headaches. Telling [11] in 1911 thought "fibrositis" in the posterior cervical region and Patrick [12] thought local infections caused headaches beginning in the suboccipital region and radiating forward. Gunther and Kerr [13] in 1929, Bisgard [14] in 1932 and Holbrook [15] in 1927 reported on groups of cases with arthritis of the cervical spine who suffered from headaches originating in the upper cervical region and having radiation to the temporofrontal areas. None of the authors related these symptoms to trauma and none noted any straightening of the cervical spine. In 1944, Jones and Brown [16] related the headache of "post-traumatic head syndrome" to some type of pathologic process in the upper part of the cervical spine but did not present any roentgenologic evidence. Little [17] in 1946 reported his experiences with a group of cases with headache previously diagnosed as postconcussion syndrome, atypical trigeminal neuralgia, migraine and hysteria. A high percentage of them showed roentgen-ray evidence of a loss of the normal cervical lordotic curvature. Raney and Raney [18] in 1948 noted headache as a frequent accompaniment of ruptured lower cervical discs, and reported cases which demonstrated a straight cervical spine by roentgen-ray. Josey [19] recently reported on 20 cases of headache thought to be related to upper cervical spine lesions. During the past three years, a group of approximately 30 cases whose presenting complaint was headache and whose symptoms and findings form a rather close pattern have been seen in my private practice.

Although these cases did not present a clearcut symptom complex, the history and physical observations presented many features of a similar nature and the roentgenograms were always characteristic. A history of trauma was usually not obtained except on direct and insistent questioning, and often was of such slight degree or so far in the past that the patient was not impressed with its relationship to headache. There was usually, but not always, a history of attacks of soreness and stiffness or "cricks" in the neck, either preceding or in association with the headache. The headaches were frequent, almost daily, and usually prolonged and recurrent for weeks or years. Most often beginning in the occipital region, with radiation to the frontal or supraorbital region, the headaches were steady and varied from a mild ache to intense pain. The frontal pain was both unilateral and bilateral. At times the frontal headache was so predominant that only after

direct questioning was any painful symptom referred to the occipital region or the neck. Headache frequently had its onset while the patient was in bed and early in the morning. The position of the head at work, any exertion which placed a strain on the neck, and driving a car were often precipitating factors. Nausea of slight degree was present only if the headache was particularly severe, and vomiting was absent. In some cases the head was held in an obviously abnormal manner, but this was never extreme. Manipulation of the neck usually revealed some resistance to extreme lateral motion, but there was no obvious spasm of the superficial musculature. In practically all cases, firm pressure with the examiner's thumb just lateral to the body of the second cervical vertebra produced pain locally, and also a radiating pain which was described as shooting through the head to the frontal or supraorbital region. When the symptoms of headache were bifrontal this phenomenon could often be produced on both sides. Such pressure would almost always reproduce the frontal headache complained of, but it would not be protracted. If the patient was suffering from headaches during the course of the examination, traction in the upward direction simply with the examiner's hands on the head almost always produced temporary relief. A roentgenogram of the cervical part of the spine in each case invariably revealed loss of the normal lordotic curvature. In most instances, roentgenographic exposures were made in three lateral positions: (1) head held comfortably erect with the eyes fixed on a spot level with the eyes, (2) in extreme flexion, and (3) in extreme extension. The roentgenograms of the normally erect positions furnished the most readily demonstrable features. In only two cases was evidence of hypertrophic arthritis in the lower cervical region seen, and this was not of extensive degree.

All of the patients underwent a complete general physical investigation, with routine examinations of urine and blood. Special examinations for the common causes of headache were carried out where there was any indication. A number of the patients had refractive errors but were wearing suitable lenses, so that eyestrain was not considered a factor. None had sinus disease. Hypertension and renal disease were absent in all cases. The psychic element was evaluated in all cases. Three cases of headache occurred in obviously psychoneurotic individuals, one of whom also showed evidence of psychopathic traits. These particular cases offered difficulties in evaluation and management. But in addition to the psychic factors the symptoms and findings of cervical spine pathology were quite evident. All cases have been followed long enough to rule out, presumably, the presence of an intracranial neoplasm.

Of this group, the following four cases are illustrative:

Case 5. A 40 year old woman, while attempting to enter a slowly moving car, was thrown to the floor on April 5, 1947. She did not appear to be injured at the time and had no specific complaints. One week later, an aching pain developed in the posterior cervical region and a sharp pain in the right supraorbital area. There

was limitation of extreme motion of the neck. Pressure of the thumb to the right of the second cervical body produced, in addition to local discomfort, a sharp supraorbital pain similar to the spontaneous headache. A lateral roentgenogram of the cervical part of the spine on April 25 showed a loss of the normal lordotic curvature, with a straight alignment from the first to the seventh cervical segment. The cervical and supraorbital pain persisted unremittingly for three weeks; during this time she received local physical therapy and wore a cervical collar constantly. There was some improvement after this, but headaches would reappear after she lay down at night and

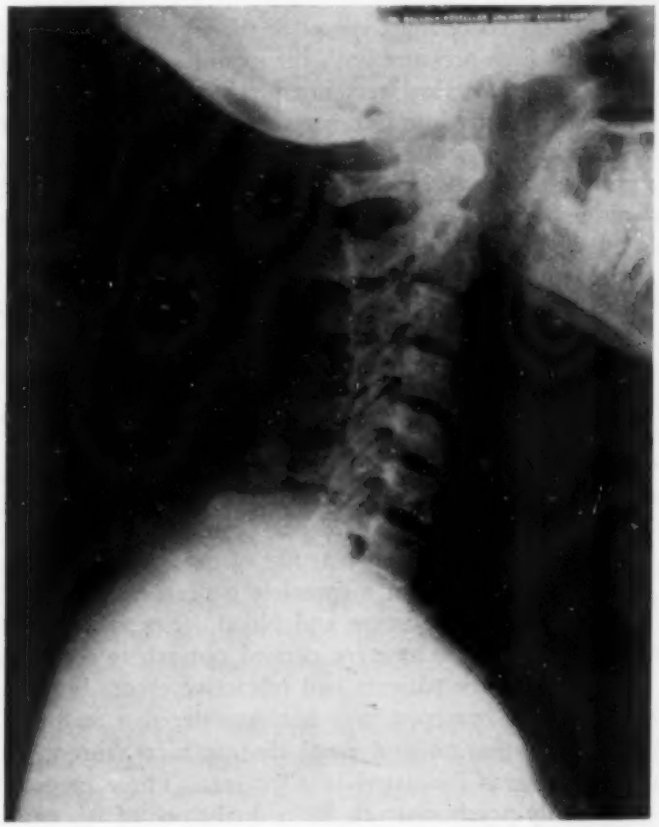

FIG. 6. Lateral cervical spine roentgenogram, case 5, demonstrating a "poker spine."

also on any excess exertion. Driving an automobile, with the necessary frequent movements of the head, would always produce an aching sensation in the neck and a right supraorbital headache. These symptoms were frequent for about three months, and necessitated the use of a cervical collar at intervals. During this period the patient would frequently awaken at night with headache and apply the cervical collar for relief. Gradually the aching in the neck and the headaches became less frequent, but even two and one-half years after the original injury the exertion of lifting any heavy object or driving an automobile in traffic would be followed by the same symptoms, which would be controlled by administration of an analgesic.

Case 6. A male draftsman, seen November 1, 1946, had had frequent headaches

as far back as he could remember. Pain was bifrontal, beginning over either eye and spreading, at times radiating to the occipital region. Attacks would occur almost daily for several months, with some periods of remission for several weeks. Onset of the headache would usually occur early in the morning, with some relief after arising and using analgesics, but the onset at times would follow physical exertion or driving a car for long periods of time. In addition, he had suffered with attacks of "cricks" in the neck for a number of years, not necessarily related to headaches. There was limitation of right lateral motion of the neck. Pressure to the right of the second cervical body produced sharp right supraorbital pain which seemed to radiate through the head. A roentgenogram on November 1, 1946 disclosed a loss of the normal

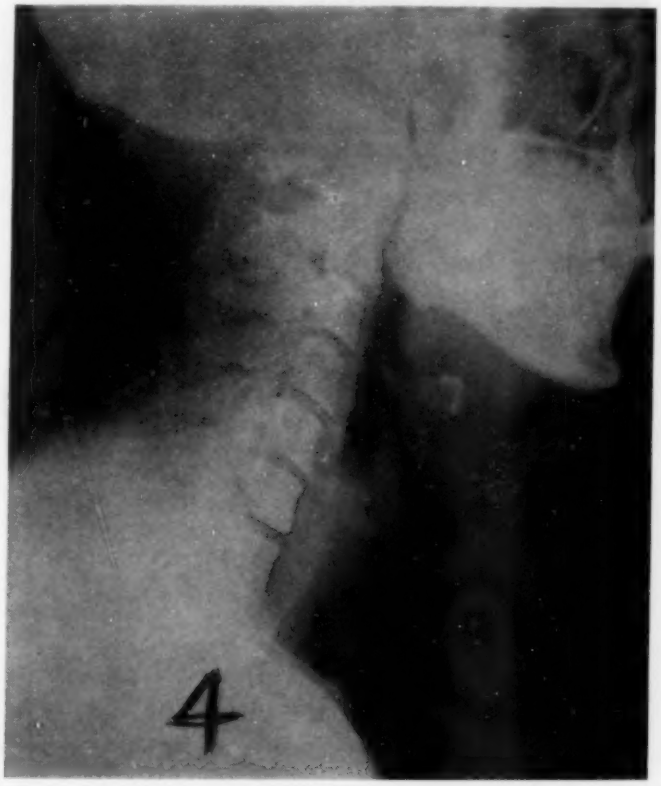

FIG. 7. Lateral cervical spine roentgenogram, case 6, showing a straight spine.

curvature, with slight anterior angulation at the fourth cervical segment. He was instructed to use a head halter traction for 20 minutes twice daily and to sleep without a pillow. For a time this gave some relief of symptoms, particularly of the neck pains, but the symptoms of headache persisted with little abatement. Various drugs were tried, including nicotinic acid, ergotamine tartrate and pyribenzamine hydrochloride. None of these had any effect. He obtained some relief with acetylsalicylic acid, with occasionally some codeine. Although the headaches were discomforting they were not incapacitating, and he did not wish to try any further or more drastic therapeutic measures. A roentgenogram of the cervical part of the spine on September 15, 1948, showed no change from the original roentgenogram.

Case 7. A 38 year old female typist was first seen December 15, 1947. At 6 a.m. December 13, severe throbbing pain had occurred in the right occipital region which disappeared in half an hour. About 1 p.m. the same day severe pain developed in the right occipital area which radiated to the right parietal and then through to the right supraorbital region, lasting two hours. Again on December 14, about 8 a.m., severe right occipital and frontal pain appeared in association with aching in the right upper cervical region, which persisted to the time of reporting to my office the next day. She admitted to an injury to her coccyx at the age of 13, but only after close questioning was the history of a recent fall elicited. On December 6 she had

FIG. 8. Lateral cervical spine roentgenogram, case 7, demonstrating a straight alignment.

fallen a short distance on stone steps, striking her chin. She was dazed for a few minutes but had no other immediate complaints. There was no limitation of motion of the neck. Firm pressure just to the right of the second cervical body produced a sharp pain in the right frontal region. A roentgenogram revealed a fusion of the fifth and sixth cervical bodies, thought to be congenital, and a straightening of the bodies of the first through the sixth cervical vertebrae. Traction applied in the office gave temporary relief of the headaches. She was instructed to use head halter traction at home for 15 minutes three times daily and to wear a cervical collar at night. She obtained considerable relief from these measures, and the persistent headache disappeared after 16 days. The headaches occurred at frequent intervals

for the next 10 weeks, and there was considerable increase associated with coughing and sneezing during an attack of coryza during the week of January 14 to 21, 1948. Up to the time of last reporting, October 15, 1948, she occasionally had a moderate headache if she was overfatigued, or if she did prolonged work at a desk with her head flexed. This headache responded to rest and administration of an analgesic. A roentgenogram taken September 27, 1948, showed a slight but far from normal degree of lordotic curvature of the cervical part of the spine.

Case 8. A housewife, aged 50, had had headaches almost daily for over 25 years. Pain was in the upper posterior cervical, occipital and bifrontal regions.

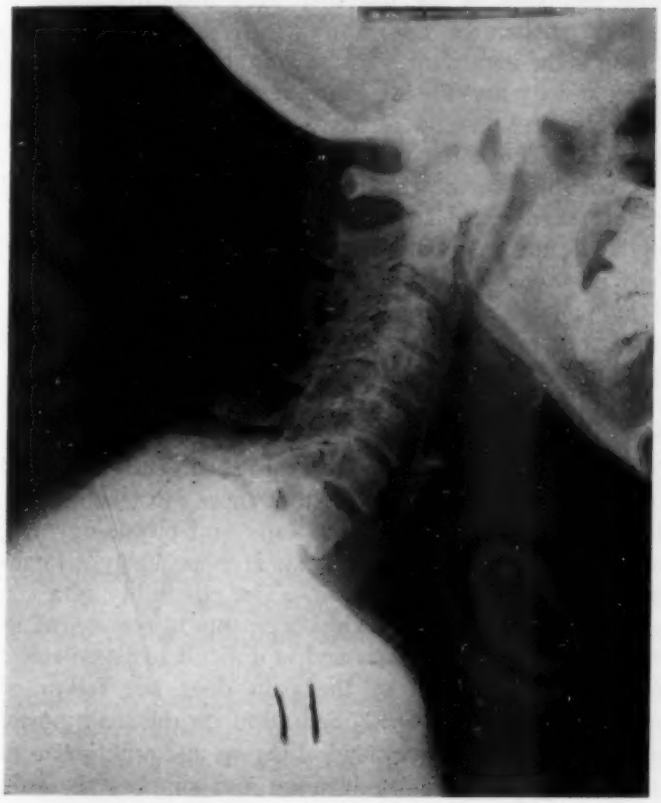

FIG. 9. Lateral cervical spine roentgenogram, case 8, showing straightening of the upper four cervical bodies, with a lordotic curve in lower portion. Some arthritic changes are present.

Occurring in the morning on awakening, they were usually less noticeable after she became active but were always made worse with excess physical exertion. She had sought relief from many physicians. In addition, she had had hay fever for many years; treatment from an allergist in the previous several years had relieved these symptoms but had had no effect on the course of the headaches. At age five she had fallen from a second story window and been unconscious for several hours. She was first examined by me on May 9, 1946. The neck was held rather stiffly, and there was definite limitation of flexion. Pressure laterally to the left of the second and

third cervical bodies produced occipital and left frontal headache. A roentgenogram showed loss of normal curvature from the first to the fourth cervical segments, and slight arthritic changes were seen. Traction with a head halter at home failed to prevent the daily headaches, and she reverted to the use of analgesics. She continued to have almost daily headaches, and prolonged rest was the only measure which produced any effective relief. A roentgenogram on September 17, 1948, showed no change from the one of May, 1948.

Discussion

From the viewpoint of the internist, very little discussion of the syndrome of lateral rupture of a lower cervical disc is needed. Recognition of the condition is the important point. This should not offer any difficulties if the symptomatology and the signs are kept in mind, particularly the variability in intensity and severity of the symptoms and extent of the range of physical findings. The lesion frequently can be localized by the symptoms and findings, but the growing experience of the neurosurgeon calls attention to the fact that there may be considerable anatomic variations and overlapping in the dermatome distribution.[6, 7, 8, 20] This, however, is of importance only if surgery is contemplated, localization can then be accurately designated by pantopaque myelography. Many of the milder cases can receive satisfactory relief by the conservative measures of a cervical collar or head traction.

The syndrome of headache associated with upper cervical spine pathology is much more difficult to understand and may or may not be real. The similarity of symptoms, physical findings and roentgenograms of the cervical spine is so close in this group of cases that there must be some correlation. The exact nature of the pathologic anatomy and physiology is not known but is thought to be traumatic in origin. It is probably a ligamentous injury, possibly in the nature of a sprain. The possibility of a ruptured disc at the levels of the upper three cervical segments is remote, as this has not been reported on an anatomic basis and is difficult to postulate on a neurologic basis. The distribution of the pain does not follow any known dermatomal or peripheral pattern. Sensation on the scalp posterior to the ears is supplied by the first three cervical nerves and anterior to that area by the fifth cranial nerve. This latter nerve also supplies the pain reference points within the cranium on the anterior surface of the tentorium cerebelli and anterior to that membrane. The under surface of the tentorium and the areas posteriorly are supplied by the ninth and tenth cranial nerves and the upper three cervical nerves. It is well known that the sensory nucleus of the fifth cranial nerve descends to the level of the third cranial segment, but it is difficult to conceive that an injury at this point would cause the symptoms. Inman and Saunders [21] produced deep and widespread pain in various parts of the human body by injections of various irritants in muscles, fasciae and ligaments and denoted it as "scleratomal" pain. Campbell and Parsons [22] produced pain in the periorbital area of man by injecting a little

6 per cent saline solution into the occipitoatlantal periarticular tissues, and both occipital and frontal pain by similar injection into the periarticular tissues of the second cervical region. These authors also designated this as "sclerotomal" distribution, and noted the areas to be closely related phylogenetically and physiologically. The significance of the straightening of the cervical spine as seen by roentgen-ray is itself not known. It is undoubtedly caused by spasm of the deep muscles of the neck, but whether this is primary or secondary is also unknown. We can understand that the loss and even at times reversal of the normal curvature of the spine is secondary to the underlying pathology and may be an attempt to relieve nerve root compression. Consideration should also be given to the possibility that the headache is simply a "tension headache" and the spasm of the deep muscles of the neck is secondary to the headache. All of these questions await a proper answer. It is hoped that further observations and investigations will furnish more satisfactory answers to the questions involved.

Treatment in these cases of headache has not been exhaustive. Many of the patients have learned to put up with their symptoms, obtaining a measure of relief from self-prescribed analgesics and added rest. The placing of a pillow beneath the shoulders while lying supine, the use of a cervical collar bandage and, in some cases, head halter traction produced temporary and in some cases semi-permanent relief. The injection of 2 per cent novocaine solution subcutaneously in the areas at the base of the skull and deep about the areas lateral to the second cervical bodies has furnished temporary relief in a few cases.

Summary

The principal features in the diagnosis of lateral rupture of a lower cervical disc have been discussed. The importance of the variability in intensity and extent of the syndrome has been emphasized as a necessity for their recognition by the internist.

A pattern of a headache syndrome associated with upper cervical spine pathology has been described. The etiology is traumatic and its exact nature unknown. The neurologic distribution of the pain cannot be correlated with known anatomic mappings and may be denoted as "sclerotomal distribution." Attempts at treatment have been mainly directed at immobilization of the head and stretching of the neck, but they have not been entirely adequate.

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PROLONGED REGULATION OF ALLOXAN DIABETES IN DOGS *

By Louis Bauman, *New York, N. Y.*, Jose L. R. Candela, *Madrid, Spain,* and Terry Martino, *New York, N. Y.*

Can continuous careful control of diabetes prevent the degenerative complications of the disease? This controversial question, though uppermost in the minds of diabetic therapists, has never been subjected to satisfactory animal experimentation.

The alloxan diabetic dog offers an approach to this problem because alloxan selectively destroys the islands of Langerhans and because the dog is best suited for this purpose.

It was planned to produce the disease and then maintain the animals in metabolism cages on the proper diet and insulin dosage for an extended period of time. Unfortunately, we were limited to a small number of animals, but the tabulated results show that the project is feasible and worthy of more extensive trial.

Experimental Procedure and Results

The caged animals were fed at 10 a.m. and 3 p.m. on an adequate commercial diet containing approximately 47 per cent carbohydrate, 27 per cent protein, 6 per cent fat and 10 per cent ash. The alloxan was injected intravenously. Urine and blood sugar estimations were usually done two hours after each feeding. Persistence of the diabetes was confirmed by glucose assimilation tests. For this purpose, 2 gm. of glucose per kilogram were given by mouth.

We lost some animals, presumably from hypoglycemia, because we were unable to maintain continuous surveillance.

The results are summarized in table 2.

The first animal (dog 611) was observed for 638 days. He failed to develop permanent diabetes after six injections of alloxan varying from 50 to 125 mg. per kg. Mild transitory diabetes followed the second dose of 100 mg. per kg.

Dog 568 received six alloxan injections varying from 69 to 120 mg. per kg. Temporary glycosuria and abnormal glucose tolerance tests were noted, but here, too, no lasting effect was achieved.

Dog 827 responded at once to 65 mg. per kg. The diabetes was satisfactorily controlled by 18 units of globin insulin. In the course of a year it was possible to reduce this to five units without relinquishing control of the disease.

* Received for publication June 30, 1950.

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Dog 610 responded quickly to a second dose of 70 mg. per kg. The diabetes was severe and not easily controlled. Satisfactory blood sugar levels were attained on 26 units of globin insulin. On the two hundred forty-fourth day of the experiment, protamine insulin was substituted for globin insulin. Death occurred after a few days, probably from insulin shock. Unfortunately, no blood sugar determination was done just before death. Careful postmortem examination revealed only an absence of the islands of Langerhans without pathologic change. It is fair to say that in this dog moderately satisfactory control was maintained during eight months without the development of arteriosclerosis.

TABLE I

"Alloxan" Diabetic Dog (Black Male)

Day of Expt.	Allox. mg./kg.	Wt. Gm.	Urine Sugar a.m.	Urine Sugar p.m.	Blood Sugars Fasting	Blood Sugars ½ hr. p.c.	Blood Sugars 1 hr. p.c.	Blood Sugars 2 hr. p.c.	Blood Sugars 3 hr. p.c.	Insulin Units Globin	Diet C. P. F.	Remarks
1	60	11,570	0		90		—				Unlimited	
3	52		0		79							
7	52		0		89							
10					92							
20	60		0		101							
21			0		113							
22					91							
27	85	11,500	0									
28			0									
30	100											
35					89			95				
38	100		+		97							
39			+		97							
40			+		121							
41			+		134							
42					101	206	220	129	118			Gluc. tol. test.
64	100				101							
66					105							
67			2+									
68			2+									
69			2+									
73					89	133	239	205	160			Diabetic curve
74			2+									
87			2+		79	146	235	223	144			Diabetic curve
90			4+									
95			4+									
119					198	331	500	301	331			Diabetic curve
120			3+									
149			4+		288	444	500	460	404			Diabetic curve
165		6,020										Diabetes uncontrolled for 4 mos., weight loss 5,480 gm.
											47 27 6 (8 a.m.)	
											94 54 12 (1 p.m.)	
168					382	431	494	500	468			Diabetic curve
169										25		
176			4+							25		
177			4+							25	47 27 6 (8 a.m.)	
178			+							20	94 54 12 (1 p.m.)	
											1,050 calories p.d.	
183			2+							20		
196			4+							20		
197										26		
199			tr.							26		
203			4+							26		
205			4+					88		28		
206			0							28		
207			+							28		
210			+							28		
211			0							28		
212			0							28		

TABLE I—*Continued*

Day of Expt.	Allox. mg./kg.	Wt. Gm.	Urine Sugar a.m.	Urine Sugar p.m.	Blood Sugars Fasting	Blood Sugars ½ hr. p.c.	Blood Sugars 1 hr. p.c.	Blood Sugars 2 hr. p.c.	Blood Sugars 3 hr. p.c.	Insulin Units Globin	Diet C. P. F.	Remarks
213		9,909	0							28		A gain of 3889 gm. in 47 days.
214			4+					75		28		
218			2+							28		
219			3+							28		
221			+							28		
225			0					87		28		
228			2+					43		28		
232			+							28		
253			2+						258	28		
254			4+					134		30		
255			2+					109		30		
257			0	0				84		30		Cataracts—postcapsular and central incipient
262		7,650	3+							30		
273										31		
281			0	0				160		31	47 27 6 (10 a.m.) 47 27 6 (3 p.m.)	
283			0					51		32		
284										31		
289-306			0	0 0						31		
310		9,313								31		
314										30		Excellent control
316			+									
325		9,313						50		31	47 27 6 (10 a.m.) 98 61 14 (1 p.m.)	
326			0	0						30		
331			0	0				50		30		
341			0	0 0				67		26		
347								62		30		
348										29		
358								69		28		
359			0	0 0						28		
369								50		26		Slight shock
424			0	0				50		25		
440								45		24		
451					264	388	444	416	294			Gluc. tol. test
454								76				
458			0							24		
462			0					54		24		
468		9,880	0							23		
481					267					23		
510		10,909	0					35		24		
517								61		23		
522		10,909		0	61					23		

This dog received 8 injections of alloxan ranging from 52 to 100 mg. per kg. in the course of 2 months before diabetes developed. The disease, though severe, was satisfactorily controlled on globin insulin. There was a gradual decrease in insulin requirement and a gain in weight.

Dog 450 was followed for 600 days. He was given 65, 75 and 100 mg. of alloxan per kilogram within 25 days. Diabetes ensued after the third injection. He was well regulated on 24 units of globin insulin per day. After 100 days protamine insulin was substituted. Regulation was fair for several months. During the last six months of the experiment, globin insulin was resumed and good regulation persisted. Weight was maintained throughout the period of observation. Autopsy was negative except for the absence of islets in the pancreas. Fundi were normal and there was no opacity in the lenses.

The sixth dog (567) reacted at once to 70 mg. of alloxan per kilogram and was satisfactorily controlled on 27 units of globin insulin for five months.

TABLE II

Summary of Results

Dog No.	Initial Weight Grams	Days of Observation	Alloxan		Occurrence of Glycosuria	Recovery from Diabetes	Globin Insulin Requirement units	Comments
			No. of Inj.	Amt. Inj. mg./kg.				
611	7,425	456	7	50–125	Transitory	Complete		
568	8,550	579	7	65–130	Transitory	Complete		
827	8,170	368	1	65	Prompt Prolonged	Partial	Gradual decrease from 18–5	
610	8,150	248	2	70	Prompt Continuous	No	20–30	
450	11,825	600	3	65–100	Prompt Continuous	No	20–29	Satisfactory regulation over a long period
567	8,600	143	1	70	Prompt Continuous	No	20–30	Satisfactory regulation
Black Male	11,570	522	8	60–100	After the 8th injection	No	20–31	Long continued satisfactory regulation

When globin insulin was replaced by protamine insulin, the morning blood sugar values were usually high and the afternoon values were too low. He probably died of insulin shock.

The last dog of the series (see table 1), a black male mongrel weighing approximately 10 kilograms, was observed for one and one-half years, that is, about one-eighth of his probable life span. He received eight alloxan injections, varying from 62 to 100 mg. per kilogram. After the third 100 mg. dose, he developed diabetes and remained untreated for three months. During this period his weight decreased from 11,500 gm. to 6,020 gm. He

FIG. 1. Alloxan dog, black male, 16 months after incidence of diabetes. Treated with diet and daily depot insulin.

then received a daily dose of from 25 to 28 units of globin insulin and regained almost 4 kg., that is, 70 per cent of the loss, in six weeks. He was regulated throughout. On the five hundred twenty-second day of observation he weighed 10,909 gm. and was in excellent shape and spirits (figure 1). The animal was then sacrificed. Complete gross and microscopic examination revealed only an absence of the islands of Langerhans. No atheroma or arteriosclerosis was discernible. The fundi were perfectly normal. A few lens opacities were noted in each eye, but they had been seen less than three months after the diabetes developed. Unfortunately, the eyes had not been examined before.

Discussion

It is obvious that dogs vary greatly in their reactivity to alloxan injections. Some are unaffected by an amount that produces severe diabetes in others. Once established, the disease is more easily controlled in some dogs than in others; this is comparable with human experience. Thorogood and Zimmerman [1] injected alloxan into 43 dogs. The amount varied from 55 to 75 mg. per kilogram. Seven developed severe and 23 developed mild diabetes. Thirteen suffered toxic renal damage.

In the course of one year the insulin requirement decreased from 18 to five units in dog 827. In the three diabetic animals that were carefully examined after death, no degenerative lesions of the eyes or vascular systems were seen. Observations on a much larger series of well controlled and poorly controlled dogs would be necessary for statistically significant results. Recently Ricketts [2] stated that such work was in progress at the University of Chicago.

A human experiment designed to answer this question would require a fairly large group of patients and many years of careful control and good coöperation. The observations of Jackson and associates [3] at the State University Hospitals of Iowa, on 75 carefully followed juvenile diabetics who had had the disease for more than 10 years, are a valuable contribution to this subject. They conclude that a high level of control delays and may possibly prevent the serious degenerative changes.

Conclusions

The response of dogs to alloxan injection is variable. Some develop diabetes after 65 mg. per kilogram; others are resistant to doses of 125 mg. per kilogram, while a third group suffers a transitory insulin deficiency. Carefully regulated alloxan diabetic dogs can be maintained in perfect health over long periods without developing any evidence of ocular or arterial disease.

The authors are indebted to the New York Diabetes Association for financial assistance, and for the pathologic examination to Dr. William Lehman, of the Surgical Pathology Department, and Dr. Ludwig van Sallman, of the Ophthalmology Department.

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NUTRITIONAL FACTORS IN CARDIAC DISEASE*

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NUTRITIONAL factors in cardiac disease will be considered from two general standpoints in this paper: (1) the importance of nutritional inadequacy in congestive failure of varied etiology, and (2) the significance of dietary factors in the etiology and treatment of atherosclerosis.

NUTRITIONAL INADEQUACY IN CONGESTIVE FAILURE

That nutritional factors may be responsible primarily or solely for congestive failure is well recognized.[1, 2, 3] An example is beriberi heart disease, a condition seen in our country mainly in the chronic alcoholic. Less stress in textbooks and the literature has been placed upon the rôle of nutritional factors as important *secondary* agents in the downward course of patients with congestive failure due primarily to non-nutritional conditions. The reasons for the development of malnutrition in the latter are multiple, and may be summarized under four general headings: (1) *Economic.* The financial burden of heart disease in many families is considerable, especially if the victim is the "breadwinner." The economic stress is often reflected in dietary restrictions which, if unwisely carried out, may have deleterious effects. (2) *Psychologic.* A marked decline in the patient's appetite may occur as a result of the emotional phenomena which almost invariably accompany the presence of heart disease. Chief among these is, of course, anxiety which centers around the uncertainty of the future for the patient, and the serious economic problems of the family. In addition, there is often a feeling of frustration due to constriction of the normal channels of emotional expression, and, in those proud individuals who dislike to be waited upon, there is the element of the revolt of the wounded ego against reality. In many instances, isolation from the family gathering at meal time, considered a kindness and a necessity by the family, deprives the patient of the potent appetite-stimulation of the communal dining-table spirit. (3) *Congestive.* Loss of appetite is a well-known manifestation of congestive phenomena in the gastrointestinal tract. The patient often learns to avoid or diminish indigestion by selecting simple foods, but these do not add to the enjoyment of eating, and in many instances they are nutritionally inadequate. Congestion may also interfere with normal absorptive processes in the intestine and thus further the development of a deficiency state. (4) *Therapeutic.* Anorexia may result from digitalis or drugs such as ammonium chloride and other gastric irritants if not properly used in the

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 9, 1951.

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treatment of congestive failure. Mercurial diuresis, often repeated, may contribute to deficiency by washing out excessive amounts of water-soluble vitamins. Much more important as a therapeutic factor, however, is the poor appetite engendered by the very low salt diets often necessary for adequate edema control. That such diets are of great value in most instances cannot be denied, but the potential effects on nutrition through discouragement of appetite must be kept in mind and dealt with as adequately as possible. (5) *Increased Metabolic Needs.* Whenever infection or hyperthyroidism are present there is an increased metabolic need, and this favors the earlier development of deficiency states under the circumstances outlined above. The great frequency with which signs of deficiency are found in cases of hyperthyroidism, even in the presence of what would ordinarily be considered an adequate intake of food, is illustrative of this point.

The result of these various factors, acting singly or in combination, is the frequent occurrence, in patients with long-standing congestive failure, of manifestations of nutritional deficiency, including hypoproteinemia, nutritional anemia, and the signs of vitamin deficiency. These developments add a very significant contribution to the cardiac difficulties already present, and thus tend to set up a vicious cycle. It is especially in that group of cases which have been referred to as "intractable heart failure" that manifestations of this type are most likely to be found, and they rank in importance along with dislocations of electrolyte pattern as factors in the resistance to the ordinary types of therapy for congestive failure.

General Inanition

The clinical picture induced by malnutrition may be that of general inanition without evidence of vitamin deficiency in those who have existed for long periods of time on a low caloric intake. The effects of such inanition have been studied in normal individuals by Keys et al.[4] Since the dietary situation in these studies was not dissimilar to that which we have found to exist in many cardiacs (as judged by dietary histories), a consideration of the findings of these investigators in relation to the problem under consideration is in order.

With prolonged periods of semistarvation a very remarkable adaptive compromise takes place in the adjustment of the body to the stressful situation. The metabolic adaptation may be summarized from the studies of Keys et al. in the following manner:

1. Reduction of Basal Metabolism.
   a. Shrinkage of the metabolizing mass of tissue. (This accounts for approximately 65 per cent of the reduction in basal metabolism.)
   b. Decreased intensity of metabolism.
2. Reduced Total Energy Metabolism.
   a. Diminished voluntary activity.
   b. Reduced cost of work (the result of reduced weight).

Such compensatory mechanisms (pseudohibernation) result in a fairly satisfactory adjustment of the previously normal individual to the effects of drastic caloric reduction. In the patient with cardiac disease or with severe hypertension, the effects of such a reduction may be distinctly beneficial for a time. Undernutrition régimes have long been advocated for the therapy of congestive failure (e.g., the Karell diet), and the benefit of such programs is probably related to the above listed effects, plus the low salt content of the diet. In hypertension, undernutrition régimes are in wide use today and definite benefit is frequently obtained. This may be due in part to semistarvation and in part to the very low salt intake.* Observations reported from Leningrad relating to the effect of semistarvation during the 1941–42 siege [5] indicated that a decrease in blood pressure was one of the characteristic symptoms observed, and similar findings were reported from other European countries subjected to famine conditions during the war.

In the long run, however, the deleterious effects of semi-starvation régimes, whether prescribed or not, may more than counterbalance the benefits originally obtained. Most serious in this respect are the hypoproteinemia and nutritional anemia which may develop. The latter is infrequent in cardiac patients, but hypoproteinemia is common in long standing congestive failure, and may be mild to moderate in degree. Plasma albumin is particularly reduced in most of these patients, with a resultant reduction of the A/G ratio, but it has not been infrequent in our experience to find reduction of both albumin and globulin with maintenance of a normal ratio. The hypoalbuminemia unquestionably contributes to maintenance of edema, and in many instances hampers therapeutic attempts to reduce it. Resistance to mercurial diuretics is evidently related to this, since responsiveness may be restored following the parenteral administration of salt-free albumin. The increased frequency with which cardiac patients having significant malnutrition are seen in the medical practice of today as compared to that of a few years ago is probably due to the extension of the life span which has resulted from more extensive and successful application of salt restriction and diuretic therapy.

That there are reasons other than nutritional for hypoproteinemia in congestive failure patients is admitted. Impairment of liver function is undoubtedly one of these.[6] The degree of albumin reduction is likely to be greatest in those patients who have had long standing and severe hepatic congestion or who have developed cardiac cirrhosis of the liver. Furthermore, marked plasma protein reduction may be seen in patients with chronic constrictive pericarditis even when they have maintained throughout their illness a good food intake, and this may well be due to hepatic insufficiency. Loss of albumin in the urine may account for some of the reduction in plasma level in many cases, but more important still is the loss which occurs into

*The dangers of rapid realimentation following semistarvation (occurrence of congestive failure, or marked blood pressure rise) are to be considered whenever a patient is allowed to return to a normal diet from a régime of severe restriction.

ascitic or pleural effusions, especially when these are large and are frequently tapped. However, the importance of the nutritional factor is indicated by the fact that therapy directed at dietary insufficiency is often effective in altering to a considerable extent the hypoproteinemia, as well as in improving the cardiac status of the patient and his responsiveness to other types of therapy.

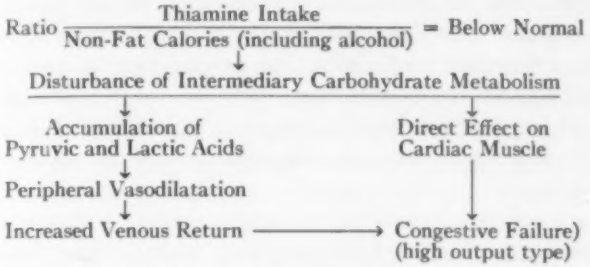
The total caloric intake is a very important factor to consider in the genesis of protein depletion. It should be well recognized that, if the caloric intake is below the maintenance level, some protein will be used for energy rather than for nitrogen needs.[7] Thus an excellent protein intake may be totally inadequate if the caloric needs of the body are not met, and, conversely, a relatively small amount of protein will be adequate if sufficient calories are supplied. This important fact is frequently lost sight of in prescribing for patients in medical practice.

Vitamin Deficiency

The frequent absence of evidences of vitamin deficiency in patients with severe caloric restriction, as considered above, is understood when it is realized that the need for coenzymes in intermediary metabolism is reduced with the reduction in total caloric intake. However, in those patients who manage to maintain a fairly good intake of non-fat calories, but derived from foods having a poor content of vitamins, there is added to the nutritional problem the element of vitamin deficiency. Alcoholic beverages are to be considered as important in this respect, since they add non-fat calories to the metabolic pool without contributing vitamins. Joliffe[8] stated that an individual consuming an adequate diet may, merely by the addition of alcohol calories, make the diet an inadequate one.

From a cardiovascular standpoint, deficiency of thiamine is of special importance. As previously stated, the full-blown primary circulatory disease due to thiamine deficiency, beriberi, is seen in this country largely in the alcoholic. There is often much difficulty in the diagnosis of this condition, but recognition may be possible on the basis of: (1) the elimination of other etiologic agents for the congestive failure; (2) the history of a diet deficient in thiamine for longer than three months, and (3) the presence of other evidence of nutritive failure, such as peripheral neuropathy or pellagra.[9] If the disease has not advanced to the irreversible stage, response to thiamine administration may be a very valuable diagnostic feature. In many cases there are evidences of rapid circulation, as manifest by a warm, flushed skin, a relatively high pulse pressure, a circulation time which is less than would ordinarily be expected with congestive failure, and special measurements showing high cardiac output ("high cardiac output failure"). These circulatory features may be related to the abnormal blood pyruvic acid and lactic acid levels found in this disease, which in turn may produce a reduction of peripheral circulatory resistance and an increased venous return to

the heart. The muscle of the latter is itself damaged by the disturbed intermediary metabolism of its own cells. The circulatory effects may then be represented schematically as follows:


Ratio Thiamine Intake / Non-Fat Calories (including alcohol) = Below Normal
Disturbance of Intermediary Carbohydrate Metabolism
Accumulation of Pyruvic and Lactic Acids
Peripheral Vasodilatation
Increased Venous Return
Direct Effect on Cardiac Muscle
Congestive Failure) (high output type)

In other forms of heart disease due primarily to non-nutritional etiologic factors, an element of vitamin deficiency is often found, and this may contribute to the circulatory difficulties already imposed upon the heart. The presence of this element in such cases is suggested by the findings of a pellagrous glossitis (a very valuable diagnostic clue) or other manifestations of vitamin B deficiency, and a dietary history indicating a deficient intake of thiamine and other members of the B group. Further evidence may be obtained by the response to therapy with intramuscular thiamine, although lack of response by no means rules out this possibility. It may be that determination of the blood lactate-pyruvate ratio will prove to be of value also in recognizing thiamine deficiency in these cases.[9]

It is important to realize that vitamin deficiency under any set of circumstances is likely to result in a lessening of appetite or total anorexia, and that a vicious cycle is thereby established. Often this will lead in time to the general state of inanition described earlier. The reëstablishment of appetite is therefore one of the goals of therapy, and for this purpose the utilization of all of the known members of the B complex, including especially niacinamide, is indicated.

Therapy of Nutritional Deficiency in Congestive Failure

The prevention and treatment of nutritional deficiency states in congestive failure patients demand a careful evaluation of all the etiologic factors, together with an attempt to eliminate or alleviate them insofar as is possible. Much can be done, especially with respect to the psychologic factors. Anxiety may often be ameliorated by encouragement and by the development of an attitude of hopefulness, even in cases with severe cardiac disease. Occupational therapy is a great boon and may work wonders in altering the psychologic patterns of discouragement and despair. Making it possible for the patient to join the family group at meal time should be attempted whenever feasible.

It is also of the utmost importance to consider the various therapeutic factors which may be responsible for poor appetite. The elimination of

anorexia due to drugs is usually, of course, simply a matter of change in dosage or form of administration, and the details of this are beyond the scope of this paper. The very important low salt diet, even in its most drastically restricted forms, may be made fairly interesting to the patient by a good dietitian who utilizes wisely the wide range of low sodium foods and condiments available, together with attractive preparation of the patient's tray. The use of salt substitutes is important, and the most desirable of these are the products which contain chiefly potassium chloride.[10] Those containing the ammonium ion are of limited value because of the loss of effect after cooking or baking.

The cation exchange resins are a very valuable addition to our therapeutic armamentarium for use in conjunction with the low salt diet. These preparations are not absorbed and exchange their cations for sodium and potassium in the gastrointestinal tract, thus permitting a greater intake of sodium without increased absorption. Those resins which contain, as ingested, both ammonium and potassium ions are desirable since they prevent the occurrence of hypopotassemia and acidosis which are occasionally serious complications of ammonium resin administration. The only disadvantage besides expense which we have experienced has been the occasional occurrence of mild rectal difficulties due to the mechanical effects of the resin in the feces. It has been possible to increase the sodium intake when the resin is administered in full dosage (15 gm. three times a day with meals) from 200 to 500 mg. to as much as 2.0 to 3.0 gm. of sodium per day without deleterious effects, and the patients have rejoiced in the increased palatability of the diet.

The attack upon an already established and fairly marked hypoproteinemia in a severe cardiac failure case resistant to the action of mercurial diuretics may require the utilization of salt-free albumin intravenously. By this means a good diuresis may be obtained, together with elevation of plasma protein levels not due entirely to concentration effects. Mercurial responsiveness may be thus reëstablished. In most instances, however, an attempt should be made to correct the protein deficiency by means of a high oral intake of protein, and there should also be an effort to supply sufficient calories so that the protein ingested will not be utilized for energy. Frequent small feedings are always of great value, since they are tolerated much better than the usual division of the day's intake into three meals.

In those patients who demonstrate evidence of vitamin B deficiency (the pellagrous tongue being an especially valuable sign), the administration of adequate amounts of the members of the B complex is indicated. Since, in severe failure, gastrointestinal absorption may not be too reliable, parenteral administration is indicated. Under these circumstances, thiamine may be given intramuscularly (the intravenous route being undesirable because of the possibility of reactions after repeated administration) in a dosage of 100 mg. per day. The fact that this amount may result in a considerable

loss in the urine, and that it may be more than is actually needed, is met with the argument that no harm is done and that there is greater certainty that the need is supplied than with lesser dosage. It is also wise to supply other members of the B complex, especially niacinamide, by parenteral route, since appetite stimulation may be obtained thereby. As soon as possible, of course, a shift should be made to oral administration of the vitamins. The effect upon the appearance of the tongue is a valuable criterion of successful vitamin therapy, though not related to thiamine effect. In some cases, however, alteration in the appearance of the tongue may not be accomplished by vitamin therapy alone. This is especially true in cases of long standing deficiency. These patients may respond only after a sufficient intake of protein and calories has been achieved. Occasionally the effects of long standing deficiency may be so severe as to defy all attempts at correction. This fact emphasizes the importance of *prevention* of deficiency in the therapy of congestive failure.

Dietary Factors in Atherosclerosis

A discussion of nutritional factors in cardiac disease would not be complete without a consideration of an effect which is not the result of deficiency, but rather of a surfeit in the intake of a particular class of foods. In recent years a rapidly increasing body of evidence has developed indicating that a disturbance of lipid metabolism, together with a surfeit of dietary fat, is an extremely important factor in the etiology of atherosclerosis. This evidence is based upon research into the geopathology and other relationships of this serious disease, upon animal experimentation, and upon studies of lipid metabolic aberrations in the human.[11] The physicochemical discoveries of Gofman et al.[12] have been epoch-making in that they have answered the objections previously raised to the lipid-disturbance theories based upon chemical determinations alone, and have shown that persons with coronary disease do demonstrate almost invariably at the time of the test the presence of abnormally large, low density lipoprotein particles in the blood. Of great practical value has been the demonstration that rigid restriction of fat intake is effective in reducing the abnormal particles in the blood stream. To date there has been no satisfactory explanation offered for the presence of this physicochemical abnormality in the blood stream of some individuals and its absence in others. The well known hereditary tendency toward the development of atherosclerotic lesions may be closely related to this defect, whatever its basic nature may be.

That the American public has increased to a very considerable extent its average consumption of fat during recent years is indicated by diagrams A and B of figure 1. Comparing the per capita consumption of food for the years 1910 and 1948, it will be noted that there has been a significant shift toward a greater intake of fat calories, with a corresponding lessening of carbohydrate sources, the protein and total caloric intakes remaining essen-

tially unchanged. The statistics for intervening years indicate a progressive trend in this direction. It is understandable that such a trend should occur in a land of plenty, since the culinary art has long recognized a direct relationship between the fat content of a meal and the gustatory pleasure and satiety derived therefrom. Statistics for fat intake in other areas of Western civilization have indicated a very similar trend, interrupted only during the war years, when fat supplies were diverted from the table to the many and heavy demands of the God Mars for glycerol and other fat products. Considerable evidence has accumulated to indicate that, when such reduction in utilization of fat has occurred, there has been a corresponding decline in the incidence of coronary accidents.

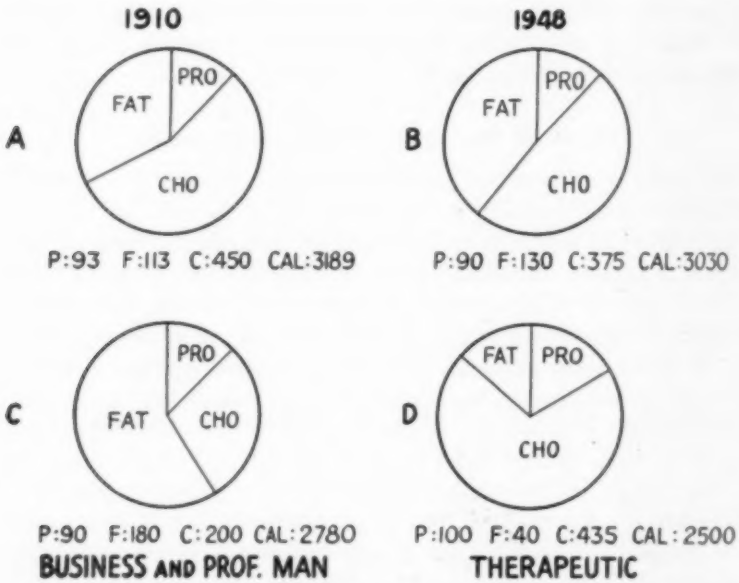


FIG. 1. A and B: Estimated average American dietary for the years 1910 and 1948, respectively. The circles are divided in such manner as to represent the percentage of total calories supplied by each of the basic food groups. The figures below the circles represent the number of grams of each food group and total calories. (From Misc. Public. 691, U. S. Dept. of Agricult., Aug. 1949: Estimated nutritive value of civilian food supply, expressed as daily quantities of nutrients per capita, after allowance for waste and deterioration.) C: Calculated average daily dietary intake of a group of business and professional men. D: Diet prescribed for average patient with coronary disease who is engaged in a sedentary occupation.

Diagram C of figure 1 indicates the far greater increase in the proportion of calories derived from fat in the dietary of a group of business and professional men considered to be average representatives of their groups. It has been well recognized that coronary disease is more prevalent in these than in the lower income groups of the country's population.

Attempts to influence coronary atherosclerosis by dietary means have been carried on by a number of investigators over the years since the ap-

pearance of the early evidence tending to incriminate cholesterol in the etiology of this disease. Throughout most of this period the attempts were based upon restriction of cholesterol itself in the diet. It became apparent, however, that, despite drastic reduction in foods containing this lipid the blood level of cholesterol was essentially uninfluenced. This has been attributed to the ability of the body to produce cholesterol endogenously whenever acetate building blocks are available.[13] Furthermore, low animal fat diets have not achieved any very appreciable clinical benefit. Only since the attempts have been directed at a drastic reduction in the total intake of fat, both vegetable and animal, have results been accomplished which appear to be in the right direction. The evidence for such beneficial effect has included: (1) reduction of the blood concentration of the group of lipoprotein molecules (S_f 10–20), shown by Gofman et al.[12] to be associated with atherosclerosis both in the experimental animal and in man; (2) the significant reduction of the blood cholesterol level in a considerable percentage of patients, and (3) apparently beneficial clinical effects. Unfortunately for the general utilization of these criteria of benefit, the first is a highly specialized technical procedure available at the moment in a limited number of clinics throughout the country. The second is widely available and of definite value, but with the limitation that the atherosclerotic process is evidently more closely related to the physicochemical lipid features of the blood than to the chemical level of cholesterol itself. The S_f 10–20 molecules may decline appreciably even without a decline in the analytic blood cholesterol level.[12] However, if an appreciable reduction in blood cholesterol is obtained and maintained (with due regard for the usual fluctuation in level observed in atherosclerotic individuals), it is probable that a definitely beneficial effect is being obtained. The third criterion is much less significant, since the spontaneous fluctuations of coronary disease manifestations make evaluation difficult in any given case. What is obviously needed is a long-term, well controlled clinical study. To date, available clinical studies have not been sufficiently well controlled to answer completely all of the possible objections that could be raised. However, the combination of the laboratory data now available, plus the clinical evidence so far accumulated, imperfect though it may be, tends to indicate that the most valuable attack available at the moment against the atherosclerotic process is the dietary approach through drastic limitation of total fat intake.

Diagram D of figure 1 demonstrates the distribution of dietary constituents which we are utilizing at the present time in the therapy of atherosclerotic disease. In some instances a reduction of fat to 25 gm. per day may be indicated, at least temporarily, depending upon the blood cholesterol levels. The total caloric intake is adjusted by means of altering the carbohydrate intake, depending upon the patient's energy needs or upon the necessity for body weight alteration. Fortunately, most persons requiring this diet are in sedentary occupations, hence the caloric needs do not often exceed 2,500 calories. Vitamin A is supplied in the form of concentrated supple-

ments. There is no evidence that supplements of the other fat-soluble vitamins are needed. It is to be noted that the protein intake is maintained at a high level, based upon the evidence that albumin acts as an important stabilizer of cholesterol sols, and hence is a possible factor in the prevention of disease.[14] The achievement of such a protein intake in the presence of a very low fat allowance is not a simple matter, since the ordinary reliance upon meats to provide a considerable portion of the protein intake is not possible, due to the high fat content of most meats even when carefully prepared. The problem is solved, however, through the utilization of fat-free milk, dry curd cottage cheese, low-fat sea foods, gelatin, etc. Of great help in the instruction of patients is the utilization of a book containing the basic principles, together with an abundance of recipes and suggestions for proper food preparation.[15]

Two important questions may be raised concerning the high carbohydrate content of the diet. The first of these concerns the fact that a considerable portion of the carbohydrate may be converted into fat in the endogenous metabolism of the body, with an end result similar to that which would obtain with a higher dietary fat intake. That this is so cannot be denied, but the fat thus formed apparently does not result in physicochemical representatives in the blood of the type associated with the development of arterial disease. The second question concerns the possibility of the development of diabetes mellitus on such a high carbohydrate régime. That this possibility has not been a significant one in practice is undoubtedly related to the fact that a high fat rather than a high carbohydrate intake is the important factor, apart from hereditary considerations, in the development of this disease.[16]

The very low fat diet is admittedly not the type that would be chosen from the standpoint of enjoyment alone. Therefore it may be difficult at times to get the patient to coöperate very long on such a régime. Success, however, is dependent upon such coöperation, and it is incumbent upon the physician to "sell" the patient upon the advantages of remaining upon the diet, and also to utilize all possible dietetic ingenuity to make the program as varied and as pleasant as possible. It is easier to convince patients in proportion to their experience with the symptoms occasioned by coronary disease. It is easier, also, to obtain maintenance of dietary coöperation in those who have continued on the diet long enough to experience the sense of well-being which often results. Furthermore, adjustment of taste to the limited régime is not infrequently achieved with time in those who can be encouraged to persist through the period of early discouragement.

The question naturally arises concerning the possible value of the low fat diet in the prophylaxis of coronary disease. It would appear that such a régime is indicated for adult males when there is a strong familial tendency toward coronary disease relatively early in life, or in whom hypercholesteremia is discovered. However, the great limiting factor in this is the

difficulty inherent in convincing a person who feels perfectly well to remain on such a program. Under such circumstances we have advised a less drastic fat restriction, hoping that this will serve as a successful compromise.

It is to be hoped that, in the not too distant future, research may provide a means of attacking the disturbed lipid metabolism of atherosclerotic patients in such a manner that they may safely enjoy a liberal fat intake. To date none of the lipotropic substances have produced significant or lasting alterations in the lipid defect, nor have other types of treatment been successful, with the exception of the dietary management described.

Summary

Two phases of nutritional disturbance in relationship to cardiac disease have been considered. The first of these concerns the ever-increasing number of congestive failure patients who have become relatively resistant to therapeutic efforts after long periods of good response. These are patients whose lives have been considerably prolonged by modern drastic salt restriction and diuretic therapy, but who have often developed, as do patients with other long-standing chronic diseases, a nutritional deficiency pattern as a complication of their illness. The nutritional factor then becomes one of the influences contributing to the difficulties of further successful management. Preferably this problem should be dealt with in a preventive manner, using every means to maintain nutrition despite the restrictions which must be imposed, and with due consideration of all the contributory factors which have been outlined. When a deficiency state has already made its appearance, successful management of the congestive failure often depends upon correction or amelioration of hypoproteinemia, nutritional anemia or vitamin deficiency states by the full utilization of all the dietetic and supplementary measures available to modern medicine.

The nutritional factor in atherosclerosis has also been considered, not because of a deficiency pattern but rather because of the etiologic significance of a surfeit of dietary fat in those persons having an inherent defect in lipid metabolism. The importance of strict limitation of the total fat intake, vegetable and animal, is stressed, with consideration of the dietetic principles involved, and especially the importance of the maintenance of an adequate protein intake.

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STELLATE GANGLION BLOCK IN CEREBRO-VASCULAR ACCIDENTS *

By William A. Nosik, M.D., *Cleveland, Ohio*

Not until a relatively short time ago was interest rekindled in a more active treatment of cerebrovascular occlusions in the hope of decreasing the degree of neurologic residua. Stress had been placed upon the desirability of good nursing care and supportive attention. Drugs of the vasodilator group received but scant mention, there being little to suggest that any lasting benefit might result from a short period of vasodilatation.

Since it appeared more logical to alter the cerebral blood supply directly in the treatment of various neurologic disorders, Royle [1, 2] suggested and performed thoracocervical sympathectomy in such conditions as early as 1932. However, because of his rather extravagant claims of clinical improvement in cases of congenital spastic hemiplegia and spastic paraplegia, lethargy of encephalitis, congenital mental deficiency, deafness and disseminated sclerosis, this work was either discounted or overlooked and eventually slipped into oblivion for many years.

In 1936, Villaret and Cachera [3] demonstrated that the vasoconstriction which followed the introduction of an experimental embolus could be abolished by cervical sympathetic nerve block. They presented two patients with postoperative embolic hemiplegia who showed marked improvement after stellate ganglion block. They believed that the zone of vasoconstriction about this ischemic or hemorrhagic area was affected by the block and that the decrease of local edema decreased the neurologic changes.

This was followed by the report of Mackey and Scott [4] in 1938, who performed stellate blocks on 19 patients with acute cerebrovascular accidents, with beneficial result in nine. They believed that patients with cerebral thrombosis or embolism, and without too extensive arteriosclerotic changes in the cerebral vessels, were the better candidates for this treatment.

No further report is noted until that of Volpitto and Risteen [5] in 1943, who presented a small series of patients with symptoms of a cerebrovascular occlusion treated by block of the stellate ganglion with novocaine. Improvement ranging from partial to complete recovery was noted. These observers also had a remarkable opportunity to observe the effects of a stellate block on the cerebral circulation in one patient. After a negative trephination, and with the cortex exposed, a stellate block was done. Within one minute of the injection, the pial vessels became engorged and a number of vessels of smaller caliber became visible. In a later report (1946),[6] hav-

* Presented before the Section of Medicine, Cleveland Academy of Medicine, November 10, 1948, and the Tri-State Neurological Meeting, September 24, 1949.
Received for publication December 12, 1949.

ing performed this procedure in 275 patients, they gave their impressions and stated their belief that the individual improvement noted varied from 30 to 90 per cent.

In a recent report, Gilbert and de Takats [7] presented 25 patients who had been treated with this method, and noted beneficial response in 19. The responses indicated a decrease in the neurologic deficit which, they believed, was accelerated by early stellate blocking.

Though it had been accepted for years that the vasomotor control of the cerebral vessels was either very weak or nonexistent, and that such alterations as did occur were secondary to cardiac output and vasomotor reactions elsewhere in the body, more recent work indicates that the cerebral vessels are responsive to sympathetic and parasympathetic stimulation even as other vessels are elsewhere. Forbes and Cobb [8] have shown that stimulation of the severed end of the cervical sympathetic trunk will produce a vasoconstriction, while stimulation of the parasympathetics, i.e., stimulation of the greater superficial petrosal nerve at the geniculate ganglion, will produce vasodilatation of the pial vessels of the parietal cortex. These authors have summarized the factors controlling cerebral blood flow in a table presented here.

Factors Regulating Blood Flow in the Brain

1. *Extracerebral:* Systemic arterial pressure. This factor, which apparently dominates all others, is subject to such influences as the vasomotor responses determined by the cardiovascular centers in the central nervous system or the carotid sinuses, by arteriolar resistance elsewhere in the body, the venous return to the heart, and the cardiac status per se.

2. *Cerebral factors:* Active changes in caliber of cerebral arteries are due to changes in tone of the arterial wall and serve to compensate for fluctuations in the systemic arterial pressure. There appears to be an inverse relationship between the caliber of the arteries and the intravascular pressure, i.e., there is a constriction of the cerebral arteries when the systemic blood pressure rises and a dilation when the pressure falls. This mechanism provides a remarkable stability in the intracranial blood flow.

These changes may be instituted by:

(*a*) Direct trauma to vessel wall.

(*b*) Chemical changes in arterial blood—CO_2, nitrites, alcohol, CO, H_2S.

(*c*) Asphyxia of tissue due to slow blood flow, which in turn may be due to low blood pressure, high intracranial pressure or vascular occlusion of cerebral vessels. However, the vasodilatation seen is not due to a neural reflex, since it is unaffected by local cocaine or atropine application, but rather represents a chemical effect on the vessel wall.

(*d*) Local neurone activity—local increase in flow. This may be due to a local increase in CO_2 or to an increase in other products of cellular activity.

(*e*) Activity of cerebral vasoconstrictor nerves (sympathetic).
(*f*) Activity of cerebral vasodilator nerves (parasympathetic).

3. *Passive changes in arterial caliber:* These changes in arterial caliber, which are transient and slight, occur when there is an abrupt fluctuation in blood pressure and are mechanical responses to this alteration.

We are concerned here largely with the effect of the local neural vasomotor control and its application to the treatment of cerebral vascular occlusions. Admittedly, the effect of the neural elements upon the caliber of the cerebral vessels is not so great as upon that of the skin. The relative response is indicated here in a comparison made by Forbes and Cobb [8] (figure 1), who also noted that constriction of venules may occur in response to stimulation of the cervical sympathetic nerve. While the pial response

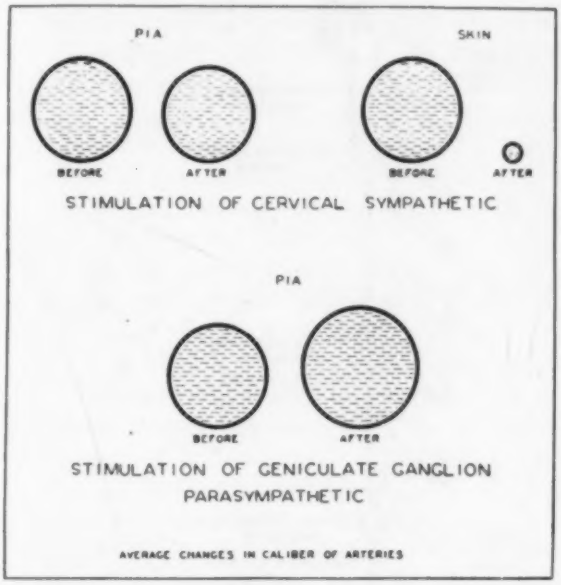

FIG. 1. (*Above*) Relative effect of stimulation of cervical sympathetic trunk on pial and skin vessels. (*Below*) Effect of parasympathetic stimulation on caliber of pial vessels. (After Forbes and Cobb.)

is only one-tenth that in the cutaneous vessels, the presence of an effective neural control over the cerebral vessels is established. Advantage is taken of this fact in the treatment of cerebrovascular occlusion by improving cerebral circulation about such an occlusion. The interruption of the neural vasoconstrictor elements by novocaine block of the cervical sympathetic chain is the basis of the treatment instituted to decrease the amount of permanent cerebral damage after such a clinical episode occurs.

The cervical sympathetic chain mentioned in this procedure consists of three ganglia joined together by an association trunk, lying behind the

carotid sheath in the neck. The ganglia are the superior cervical, the middle cervical and the inferior cervical or stellate ganglion, which may be fused with the first thoracic. The numerous branchings of the plexus from these ganglia are all postganglionic, since this part of the sympathetic system receives no white rami communicantes. The preganglionic fibers travel upward from the thoracic region to a synapse in these ganglia with the postganglionic fibers, which then continue upward as a plexus to participate in many interconnections. The plexuses of greatest interest here are two

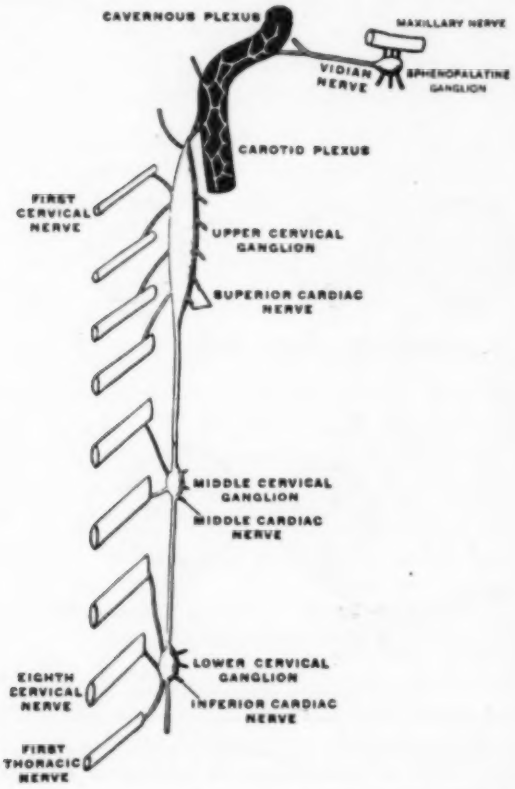

FIG. 2. Schematic drawing of cervical sympathetic anatomy.

in number: The first (the cerebral carotid nerve) originates in the superior cervical ganglion and consists of a large plexus which surrounds the internal carotid artery. It accompanies this vessel in its intracranial course to its terminal divisions in the brain. The second (the vertebral plexus) consists of a plexus about the vertebral artery and has its origin in the inferior cervical ganglion, i.e., the stellate ganglion (figure 2).

To paralyze the cerebral vasoconstrictor nerves on the same side, novocaine is injected about the cervical sympathetic chain. It is something of a

misnomer to term this a stellate ganglion block, since for technical reasons it is more likely a block of the cervical chain than the stellate ganglion itself. Various methods of blocking the stellate ganglion area have been tried and discarded in favor of the method of de Sousa Pereira.[9]

In this method, the area of the sympathetic chain is infiltrated between the stellate ganglion and the middle cervical ganglion. The novocaine is then massaged downward to envelop the region of the stellate ganglion. Advantage is taken of the disposition of the cervical fascia. The infiltration is made deep and is confined beneath the plane of the fascia colli to surround the sympathetic ganglia and the interconnecting chain. To perform this block, the patient may be in either the sitting or the lying position. The injection is made into the cervical region on the same side as the lesion, that is, on the side opposite the paralysis. With the neck slightly extended and the chin rotated a bit to the affected side, the transverse process of the sixth cervical vertebra is palpated. The finger is pressed tightly against the structure and the deep vessels retracted medially as far as possible. A number 20 or 22 needle, affixed to a 10 c.c. syringe containing 1 per cent novocaine solution, is then introduced to encounter the transverse process of the sixth cervical vertebra as far medially as is conveniently possible from the anterolateral approach. Frequently the patient may complain of diffuse dull pain in the scapular region. With the needle pressed tightly against the transverse process, the retracted deep vessels are released and careful aspiration test is made. If no blood, spinal fluid or air returns, 10 c.c. of novocaine are slowly injected and the needle withdrawn.

Within a matter of a minute or so, a slightly increased moistness of the eye will be noted. This is then followed by a conjunctival injection, miosis, ptosis and a dryness of the forehead and cheek as well as a redness of the ipsilateral face and ear.

It is stressed that aspiration should be done before the injection is begun because the needle might inadvertently enter a vessel or, worse, might enter the dural sheath of a cervical nerve and so be injected subarachnoidally with serious result. Using this technic, it is unlikely that a pneumothorax can be produced, though this may occur when some of the other approaches to the region of the ganglion are utilized.

In what patients should the stellate ganglion block be used? I am unable to state unequivocally that all patients with a stroke are candidates for this procedure, because the experience is not yet large enough. However, in agreement with previous reports, my opinion is that those patients who have had an embolic or thrombotic cerebrovascular occlusion are more likely to derive benefit from this procedure at little risk to themselves than are those with a cerebral hemorrhage. Naturally, the earlier the block can be performed the better the possibility of forestalling associated anoxic changes in the neighboring cerebral tissue. However, improvement has been noted in some patients whose initial cerebral insult has occurred even

months previously; though, generally speaking, the longer the lesion has existed the smaller is either the possibility or the degree of objective improvement obtainable. When an improvement occurs, even in a limited degree, immediately after a block is performed, it is believed that this patient stands a better chance to be further improved by more blocks than does the patient who shows no immediate effect.

It is not always possible to differentiate between cerebral hemorrhage, embolus or occlusion in the individual case. There is presented here a sketchy table as outlined by Volpitto and Risteen (figure 3). In brief, this table serves to cover some of the salient features in each of these entities, though naturally great variations exist in the mode of onset, the subjective symptoms and objective findings in the clinical analysis of the individual patient.

TABLE I

Diagnostic Features of Cerebral Hemorrhage, Embolus and Thrombosis
(after Volpitto and Risteen)

	Hemorrhage	Embolus	Thrombosis
Warning	Usually short	None	May be over long periods
Shock nervous	Moderate	Marked	Usually slight
Loss of consciousness	Usual	Usual	Only in large occlusions
Convulsions	Rare	Rare	Fairly common
Objective findings	Develop rapidly	Develop rapidly	Develop slowly

Greater elaboration upon the differential diagnosis of cerebrovascular lesions is not within the scope of this discussion, as it is obviously a subject requiring much more space. However, mention should be made of the use of lumbar puncture. This procedure should be done in the patient whose history is suggestive of a cerebrovascular lesion. The spinal fluid is usually clear and under normal pressure in patients with cerebral embolus or thrombosis, while a greater percentage of patients with cerebral hemorrhage are apt to have a bloody fluid under pressure. Since the patient with acute cerebral hemorrhage seems to have the least favorable response to stellate blocking, the spinal fluid examination may help the clinician decide upon the advisability of using this treatment. Though the possibility of increase in cerebral hemorrhage conceivably exists, Volpitto recently stated that he does not believe that the use of stellate ganglion blocking in acute cerebrovascular hemorrhage is contraindicated.

The use of stellate ganglion block in cerebrovascular lesions does not alter

the state of those neurones which are irreversibly damaged by anoxia, but rather is directed toward those cells included in the zone of vasospasm surrounding the affected area which are capable of being revived. The sparing of these cells, which would eventually die of anoxia, permits a greater degree of neurologic recovery. A collateral circulation can be developed about the lesion, thereby limiting its extent, by paralyzing the vasoconstrictor fibers and permitting maximum vasodilatation of the arterioles. Since the venules may likewise be affected by this procedure, the development of secondary edema may also be limited. That these events occur is evidenced by the prompt transient improvement frequently noted clinically. When such transient improvement occurs immediately, the prognostic outlook is better for an ultimate permanent improvement in the neurologic deficit than if no such change occurs. However, in the patient with an extensive cerebrovascular lesion or one located in or near the vital centers, a fatal issue may not be averted even though a transient beneficial effect may have been observed after a stellate block. It is accepted that a rapid and near-complete recovery may occur after a cerebrovascular accident with no treatment other than symptomatic. However, the prompt though often transient change noted frequently within minutes of a cervical sympathetic block is regarded as more than a coincidence, particularly when a degree of improvement is maintained after each of a series of blocks. Advantage is taken of the change effected, and the blocking is continued once or even twice daily until no further improvement is noted. Where a favorable response is noted, and it is believed that a prolonged series of blocks will be necessary, it might be better judgment to excise the superior cervical ganglion surgically early in the recovery phase, if the patient's condition permits.

While this discussion has been directed to the cerebrovascular aspects of the individual's problem, it is not to be inferred that the medical maintenance of the patient's general welfare is in any way altered. The necessity for close supervision of the cardiac, respiratory, nutritional and eliminative functions, as well as good nursing care, is not obviated by performing a stellate block.

By instituting early a treatment with stellate block in patients with cerebrovascular occlusions, a close coöperation between the neurologist or neurosurgeon and the internist may result in the greater decrease of neurologic residua and a lessening in the degree of the patients' permanent disability. This treatment should be considered when such a clinical problem is encountered so that an eventual proper evaluation can be made concerning its effectiveness.

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RECENT ADVANCES IN PULMONARY RESECTION IN THE TREATMENT OF TUBERCULOSIS *

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PULMONARY tuberculosis is not a static disease but, like the god Proteus, is characterized by ever-changing manifestations. Recent successes in the excision of tuberculous lung tissue, combined with streptomycin therapy, has given increased recognition to the importance of the protean nature of this disease. Briefly, the sporadic efforts directed toward pulmonary resection prior to the advent of streptomycin occasionally achieved a brilliant result, but the overall results were generally poor. Sweet's [1] series of 63 patients treated by lobectomy or pneumonectomy, reported in 1946, may be taken as representative of the best results obtainable at that time in this country. Of 27 patients treated by lobectomy, 26 per cent were dead either as a result of the operation or of progression of the disease in one or more years after the operation. Of 36 patients treated by pneumonectomy, 39 per cent were dead either as a result of operation or of progression of the disease in one or more years after operation. Few patients in his report were more than two years postoperative. In discussing Sweet's paper, Strieder [2] indicated that, in his experience, reactivation or spread of the disease followed lobectomy in 60 per cent and in 45 per cent of the patients treated by pneumonectomy. A subsequent report by Sweet [3] revealed that by August, 1948, one-third of the patients on whom lobectomy had been performed were dead, and that 44.4 per cent of the total were apparently well. In the pneumonectomy group, 52.8 per cent of the patients were dead and 38.9 per cent were apparently well. This end result study comprised a three to seven year follow-up. Sweet's earlier report indicated to us that enthusiasm for pulmonary resection in tuberculosis was not warranted. In 1947 only nine tuberculous patients were treated at Fitzsimons General Hospital by lobectomy or pneumonectomy. However, with the advent of adequate quantities of streptomycin, we have carried out excisional surgery in an increasing number of patients with gratifying results. Certain fundamental features which have contributed to the recent advances in extirpative surgery in pulmonary tuberculosis will be presented.

The one common denominator available since 1947 and not previously obtainable is streptomycin. Certain additional chemotherapeutic agents,

* Read before the Regional Meeting, American College of Physicians, Denver, Colorado, February 21, 1950. Received for publication July 14, 1950.

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such as para-aminosalicylic acid and tibione (T.B.–1), are now being used. Our experience with the latter agent has been too limited to permit of evaluation. Penicillin, sulfa drugs, adequate quantities of whole blood, and improved anesthesia methods and operative technics have been important adjuncts. However, we believe the single most significant factor concerned in any recent advances in this field has been streptomycin. Recently, the combination of streptomycin, 1 or 2 gm. every third day, plus para-aminosalicylic acid, 12 gm. daily, has proved highly beneficial in preventing the development of resistant strains of the *Mycobacterium tuberculosis*, and equally as effective as similar daily doses of streptomycin. This combined therapy with various antimicrobial agents is now the treatment of choice when such adjunctive treatment is required.[4]

A second significant factor, which has not been generally applied in previous studies of pulmonary resection in tuberculosis, is extrapleural thoracoplasty in conjunction with extirpative surgery. Except for the

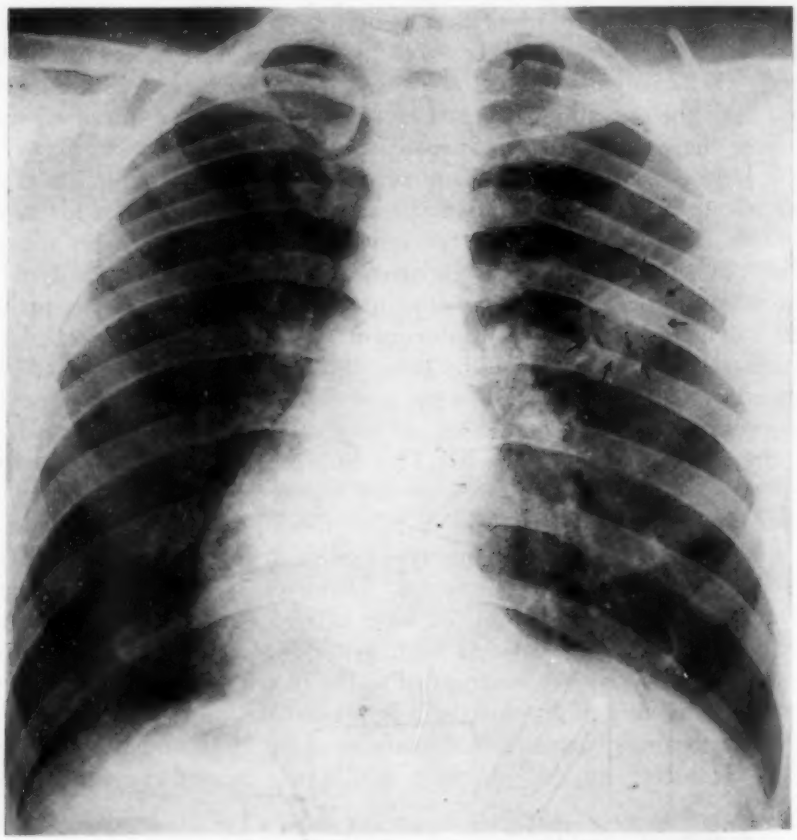

FIG. 1. *Case 1.* Slit-like translucency (Mahon sign) at border of rounded area of density, indicative of cavitation in tuberculoma.

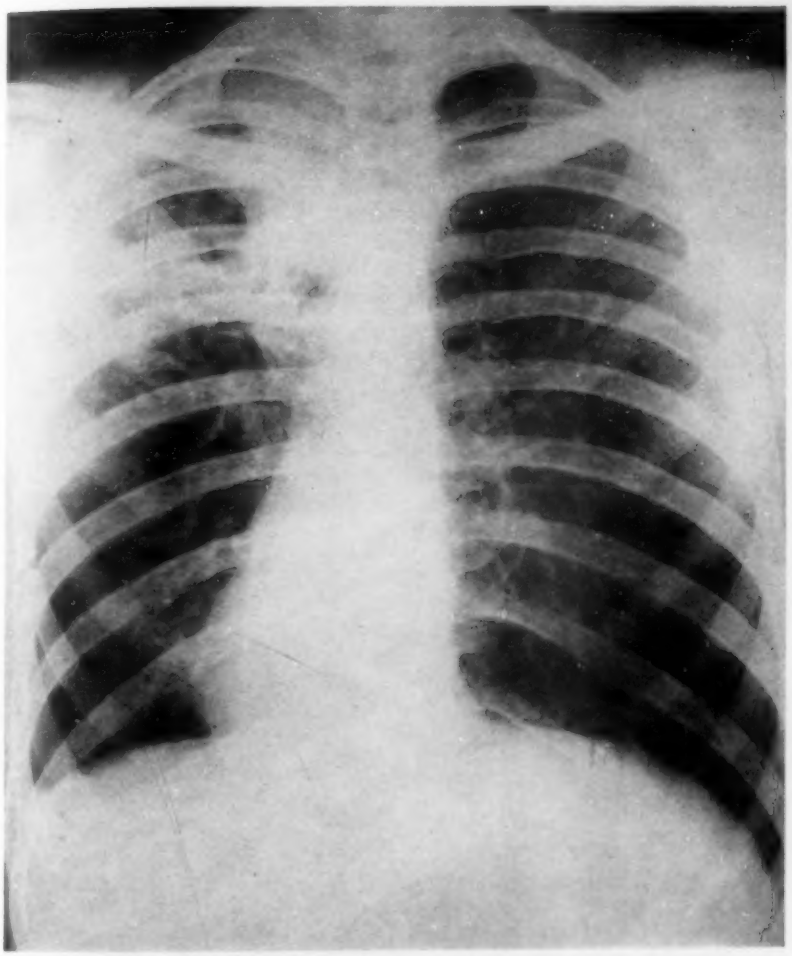

FIG. 2. *Case 2.* **Large cavity, left upper lobe, with parenchymal infiltration and moderate extension on right. Cavity failed to close after thoracoplasty, and lobectomy was performed with excellent results. See figure 3.**

focalized lesions (tuberculoma), it has been our experience that nearly all patients on whom excisional surgery other than pneumonectomy has been performed have in the remaining lung tissue a few or numerous palpable nodular tuberculous lesions.[5] The effect of overdistention of the remaining lung tissue on these active or latent foci is, as Chamberlain [6] emphasized, undesirable. To overcome this overdistention, we have adhered strictly to the principle of decreasing the size of the hemithorax in all proved cases of active pulmonary tuberculosis by thoracoplasty prior to lobectomy. Those unproved cases which, on histologic examination of the excised tissue, proved to be active tuberculosis have often been followed by thoracoplasty. The method used to accomplish this decrease in size of the hemithorax has,

in most instances, been as follows: A first stage thoracoplasty, with removal of the upper two and one-half ribs, is followed in three weeks by an upper lobectomy. At this time the fifth rib is removed, and in another three weeks a second stage thoracoplasty is done, with the removal of the remaining anterior segment of the third rib and a long posterolateral segment of the fourth rib. The result is a five-rib upper thoracoplasty and an upper lobe lobectomy. Presently, we are completing a two stage, five-rib upper thoracoplasty prior to lobectomy, or resecting the anterior segment of the third rib, and the fourth and fifth ribs at the time of upper lobectomy. In lower lobe lesions treated by lobectomy, temporary paralysis of the hemidiaphragm precedes or accompanies lobectomy. In unproved cases, phrenemphraxis is added when the diagnosis of tuberculosis is confirmed by histopathologic

FIG. 3. *Case 2.* Residual cavity in thoracoplasty collapsed lung. (Cavity filled with cotton.)

studies. We are presently studying a group of patients to evaluate the feasibility of upper phase thoracoplasty preceding lower lobectomy. It may be tenable, and is certainly logical when questionable upper lobe lesions threaten reactivation at a later date.

Indications for pulmonary resection are not, in our minds, clearly defined. Much study and research are yet to be accomplished before the type of pulmonary lesion which can best be treated by excision is determined. However, considerable progress has been made during the past three years, and we are well prepared to say which types of tuberculous lesions respond least

favorably to more conservative measures. Obviously, the attack upon the local manifestations of the disease must include a complete consideration of the patient and his disease, including the probable duration of the pulmonary lesion (new, old or mixed lesions); the reversibility of the lesions (resolving or nonresolving); the destruction of the lung tissue (site, size

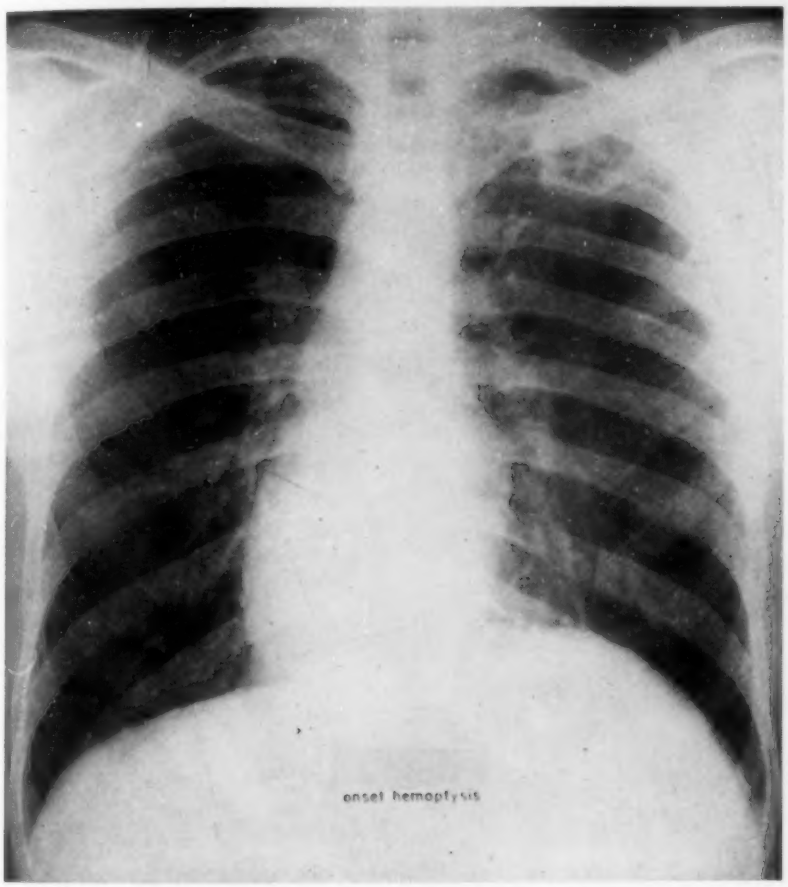

FIG. 4. *Case 3.* Recent new lesions, right upper lobe, with cavity. Lobectomy and thoracoplasty, five ribs, with streptomycin preparation and protection selected as therapy of choice. Excellent result.

and duration of cavitation); the extent and localization of the disease (lung, lobe or segment), and the type and severity of associated lesions of the bronchi and pleura. These considerations may be summarized as follows: It is axiomatic that old lesions are more safely removed than new lesions. It is appropriate, therefore, to use conservative measures for a reasonable period, six to 12 months or more, to improve the operability of the patient.

If a neoplastic lesion is suspected, a waiting period is not justified. Persistent, active, irreversible lesions require surgical intervention. Cavitation uncontrolled by conservative measures is best treated surgically. Persistent cavitary lesions following thoracoplasty require excision of the lobe or lung. With increasing experience we have gradually extended the indications for extirpative surgery. Thus, large apical, basal, hilar, large peripheral and multiple cavities or destroyed lung make it desirable to use primary excision combined with thoracoplasty and streptomycin protection as the treatment

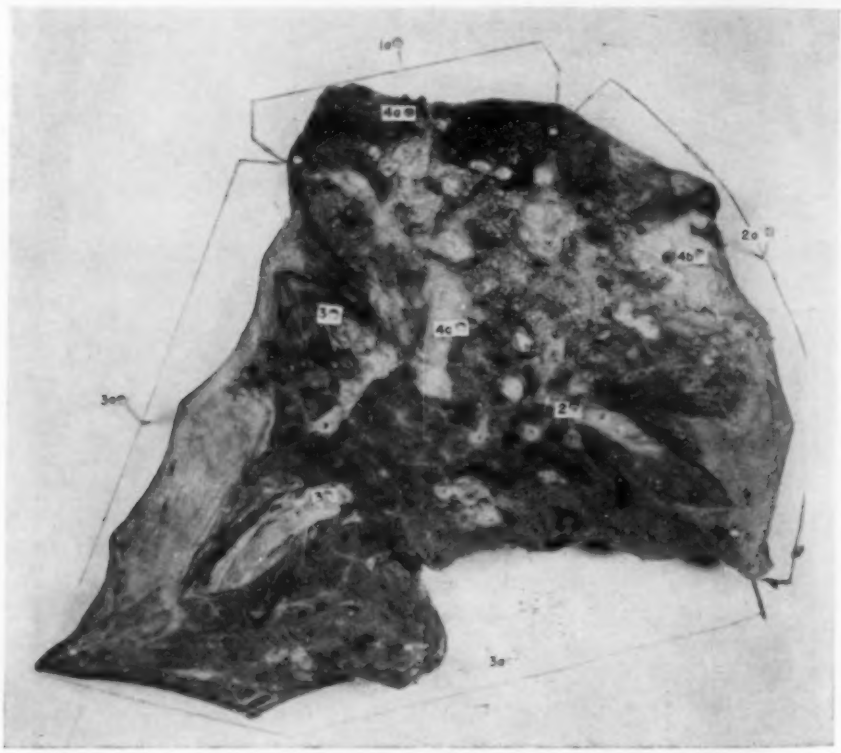

FIG. 5. *Case 3.* Surgical specimen, right upper lobe, approximately two-thirds of the lobe extensively involved.

of choice. Cicatricial tuberculous bronchostenosis is considered a definite indication for resection, but it is quite important that ulcerative and hyperplastic lesions be ruled out or controlled prior to extirpative surgery. The amazing results of streptomycin in the treatment of tuberculous endobronchial disease have revolutionized the management of this manifestation.[7] Likewise, active pleural lesions, such as empyema or marked pleural fibrosis, must be taken into account in planning treatment. Decortication is being employed more frequently in association with pulmonary excision.[8] With

these general concepts in mind, the following types of problems fall into the category of good cases for pulmonary resection:

1. Tuberculoma.
2. Thoracoplasty failure.
3. Certain fibrocavernous lesions, upper or lower lobe, not suitable for permanent collapse therapy.

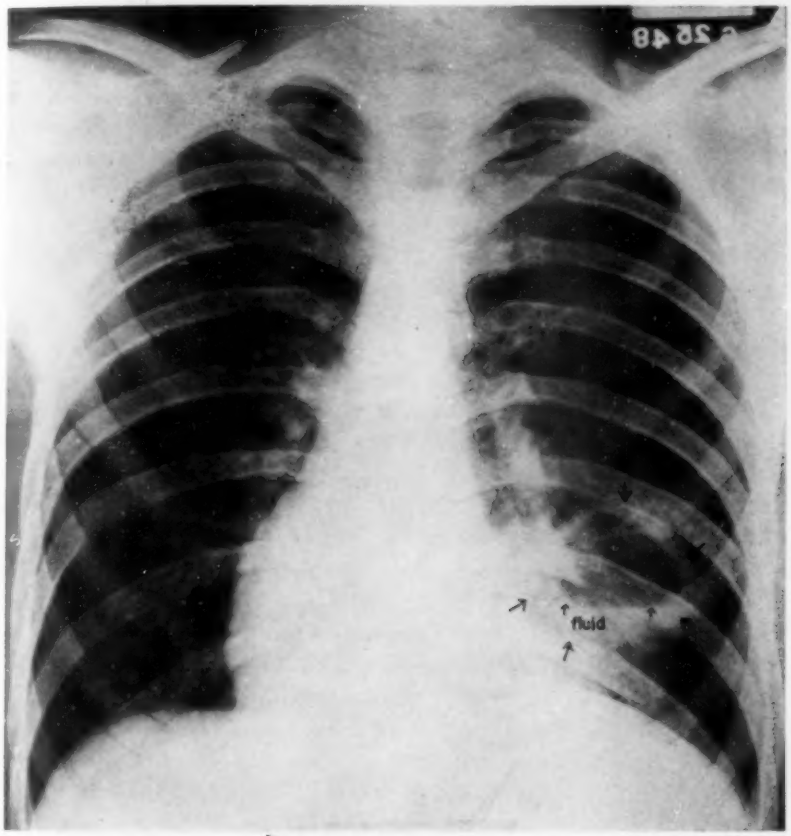

FIG. 6. *Case 4.* Lower lobe cavity. Lobectomy with streptomycin preparation and protection selected as therapy of choice. Excellent result. See figure 7.

4. Bronchial stenosis.
5. Certain pleural lesions which require decortication in addition to pulmonary resection.

CASE REPORTS

Case 1. A routine roentgenographic examination of the chest of a 25 year old white male revealed a 1.5 cm. rounded lesion in the lower portion of the upper lobe lung field. The patient was asymptomatic, but the lesion increased in a few months

to twice its original size and a slitlike area of translucency (Mahon sign) appeared (figure 1). Bronchoscopy was negative; tuberculin skin tests were negative; coccidioidin skin test was 1 plus. Sputa and gastric washings were repeatedly negative for acid-fast bacilli. The lesion was removed by wedge excision in January, 1946. It contained a slitlike cavity, 2.0 cm. long, 0.1 to 0.6 cm. wide, and culture from its caseous center was positive for acid-fast bacilli. This lesion was a ripe or mature tuberculoma which had softened and cavitated. The patient has remained well and is working. The development, fate and dangers of this lesion (tuberculoma) have

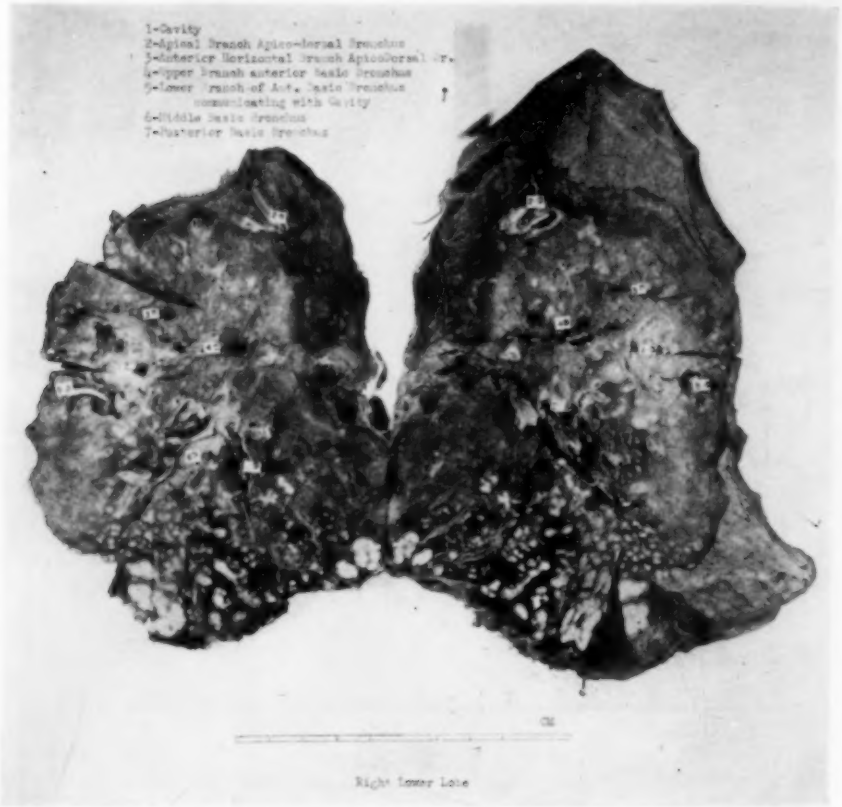

FIG. 7. *Case 4.* Surgical specimen. Tuberculous lesions more extensive than suggested by roentgenogram. See figure 6.

been described by us elsewhere.[5] Its potential and actual dangers compared with the safety of operative removal have established it as a definite indication for extirpative surgery.

Case 2. A 20 year old premedical student had noted a moderate productive cough, weight loss of 15 pounds in six months, and a recent pulmonary hemorrhage prior to admission to Fitzsimons in February, 1948. Sputum was positive for acid-fast bacilli. Roentgenograms of the chest revealed an 8 cm. cavity in the left upper lung field, with moderate exudative parenchymal infiltration and moderate infiltration extending from the level of the fourth rib anteriorly upward on the right (figure 2).

Moderate bronchogenic spread to the left lower lobe occurred following a 500 c.c. episode of pulmonary bleeding March 8, 1948. On March 13 streptomycin, 1 gram daily, was started, and considerable resolution of the soft lesions occurred in 60 days. Bronchoscopy revealed a normal tracheobronchial tree. A seven-rib left thoracoplasty, performed in three stages, was carried out between May 13 and June 24, 1948. The postoperative course was uneventful. Streptomycin was discontinued after a total dosage of 134 gm. given over an equal number of days. Frequent sputa examinations were negative for a time after operation, but sputum conversion was not

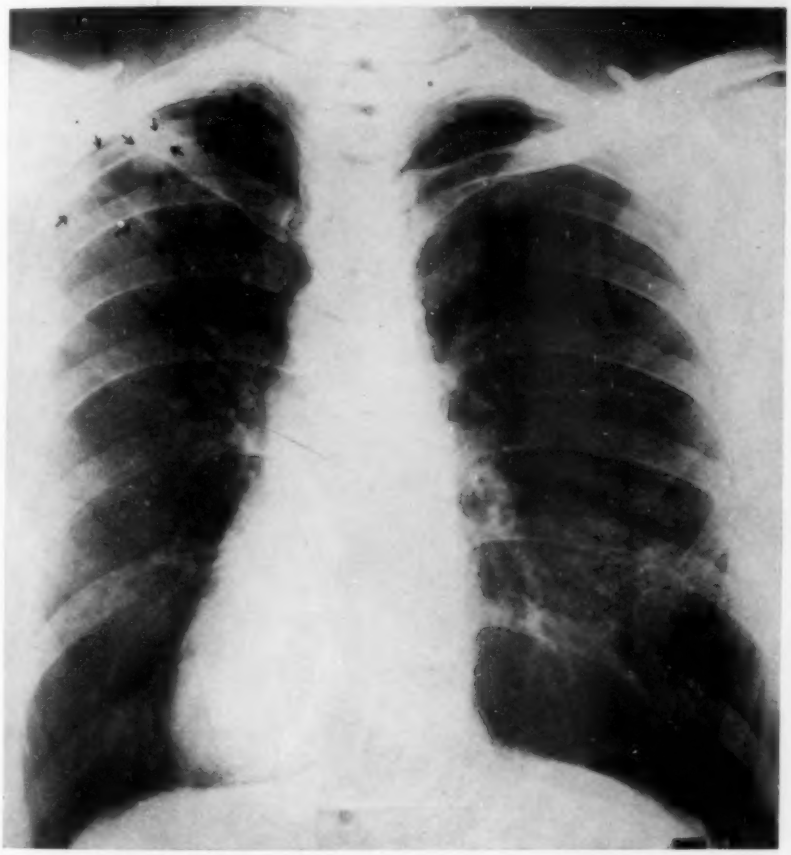

FIG. 8. *Case 5.* Long-standing disease, left upper lobe. Sputum negative. Segmental resection performed, acid-fast bacilli cultured from lesion.

permanent, and laminagrams revealed a probable cavity beneath the thoracoplasty. A left upper lobectomy was performed May 5, 1949. The lobe contained cavitary and ulcerocaseous lesions (figure 3). The sputum has been repeatedly negative since lobectomy, and the patient's prognosis is good.

Such a large cavitary lesion often fails to respond by sputum conversion following adequate thoracoplasty, and pulmonary resection now offers a most gratifying result in a high percentage of such instances of thoracoplasty

failure. Probably the principal indication for lobectomy or pneumonectomy prior to the advent of streptomycin was thoracoplasty failure, excisional surgery in most instances being reserved as a last resort procedure after all other methods of management had failed. Today, excisional surgery in combination with thoracoplasty (five ribs) is, in our experience, being

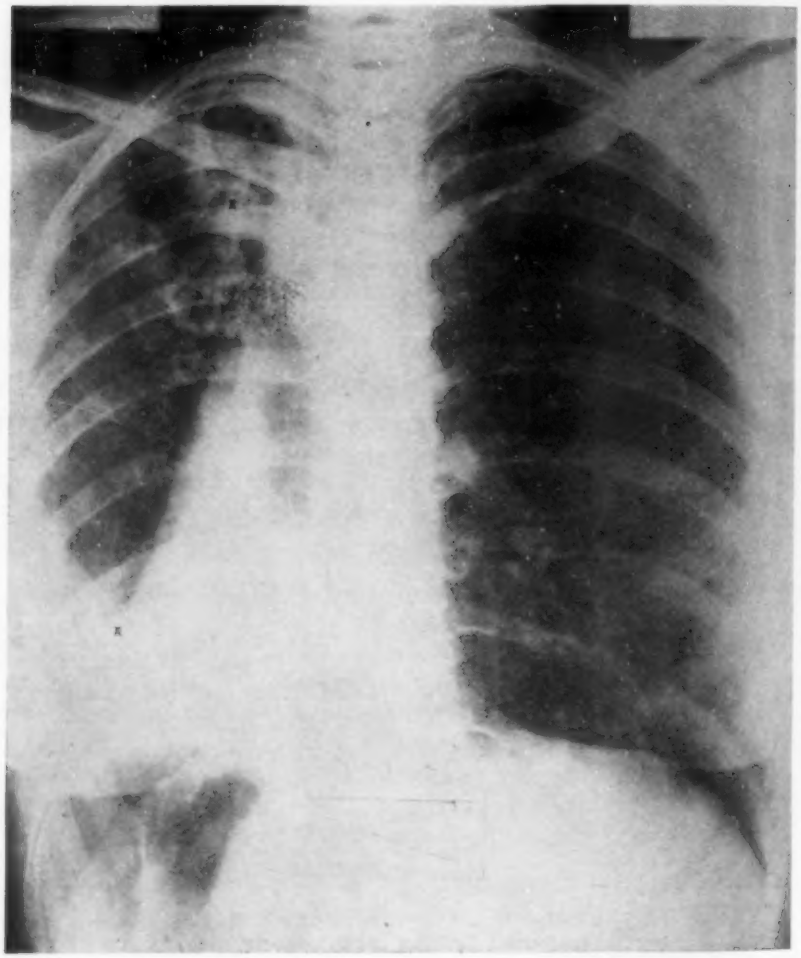

FIG. 9. *Case 6.* Extensive long-standing disease with multiple cavitation and bronchostenosis, left. Pneumonectomy employed as method of choice. See figure 10.

employed as the procedure of choice in approximately three-fourths of all patients, exclusive of tuberculous empyema, formerly considered suitable for extrapleural thoracoplasty. Final evaluation of this changing concept must await end results three to five years hence.

Case 3. A 25 year old white soldier had an abrupt onset of hemoptysis associated with mild constitutional symptoms August 18, 1948. His sputum was positive for acid-fast bacilli and on September 9 he was admitted to Fitzsimons. Streptomycin, 1 gm. daily, was administered from September 27 to October 25. The new diffuse lesions with cavitation, right upper lobe, demonstrated by chest roentgenogram (figure 4), proved to be largely irreversible tissue changes (caseous bronchopneumonia) by a period of conservative management. The patient was appraised of the findings and advised to have a right upper lobectomy and a five-rib thoracoplasty (figure 5). This was accomplished between January and March, 1949. It is ac-

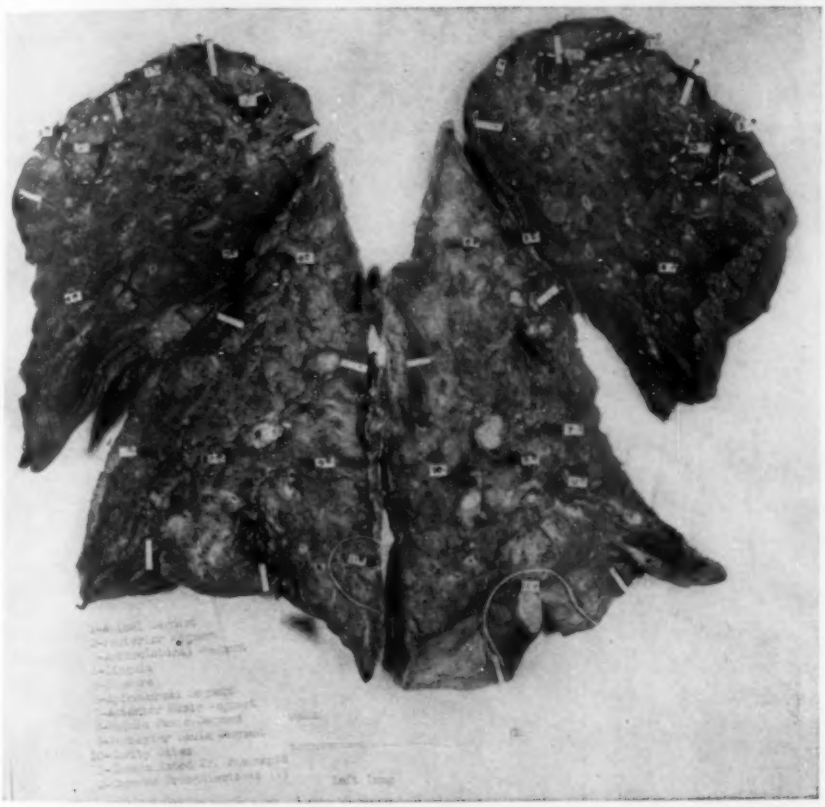

FIG. 10. *Case 6.* Surgical specimen, left lung. Extensive disease throughout. See figure 9.

knowledged that a prolonged rest regime (three to five years) may have resulted in an arrestment of the disease, or thoracoplasty alone might have been sufficient. One year postoperatively, the patient is asymptomatic, his sputum is negative, and a most favorable prognosis is predicted.

Case 4. A 20 year old white soldier was diagnosed as having pulmonary tuberculosis with a large cavitation in the right lower lobe in June, 1948, and was admitted to Fitzsimons one month later. Between June and October the patient received 91 gm. of streptomycin. Lobectomy, right lower lobe, and phrenemphraxis were performed September 30. Sixteen months postoperatively the patient is asymp-

tomatic, his sputum is negative since operation, and he has been discharged from the hospital as having received maximal benefit from hospitalization. A favorable end result is anticipated (figures 6 and 7).

On several occasions during the past two years we have been confronted with the problem of the management of suspected but unproved pulmonary tuberculosis by resection of the involved lung tissue. All are familiar with the fact that many individuals spend years as semi-invalids because of the

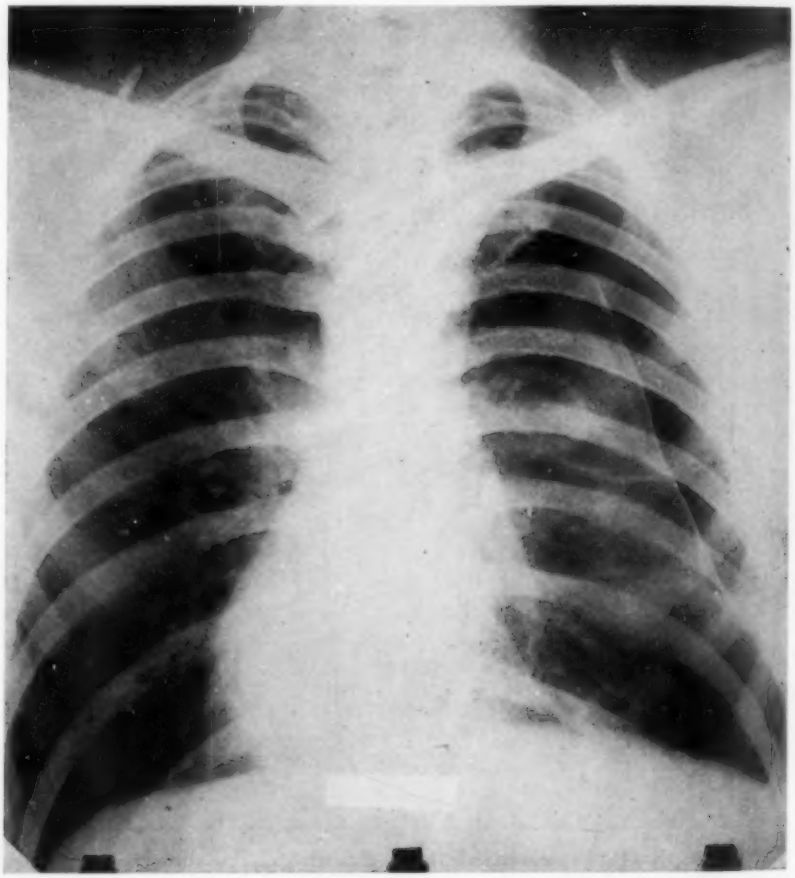

FIG. 11. *Case 7.* Cavitary lesion, right upper lobe, with unexpansible ineffective pneumothorax. Decortication and upper lobectomy. Excellent result. See figure 12.

presence of tuberculous lesions which change little, if any, over a period of years. They are wisely warned not to engage in the usual normal activities of a healthy person and to lead a very protected life. We feel that such relatively localized lesions require excisional surgery and are followed by complete rehabilitation. Segmental resection is particularly useful in these cases. The following case report is an example:

Case 5. A 40 year old physician had had a known lesion in the left upper lobe since 1944. His sputum and gastric washings had been negative on numerous examinations. In July, 1948, he again found it necessary to give up his active practice because of fatigue, slight weight loss and afternoon fever of 99° to 99.6° F., and he was admitted to Fitzsimons. The lesions had changed little, if any, in roentgen-ray appearance since first noted (figure 8). At operation, performed November 3, a segmental resection was performed preserving the large lingula division of the upper lobe. Many tubercle bacilli were found in the excised tissue. He received a total of 80 gm. of streptomycin. One year postoperatively he is symptom-free and is carrying on his practice with moderate restriction.

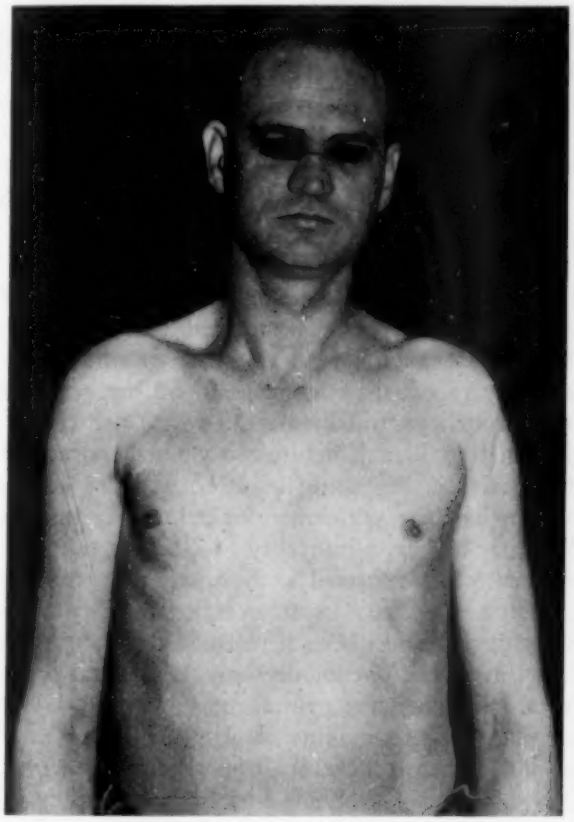

FIG. 12. *Case 7.* Post lobectomy and thoracoplasty, five ribs, right. Minimal deformity.

Case 6. A 42 year old female gave a history of known pulmonary tuberculosis since 1944, with long sanatorium treatment, massive doses of streptomycin since August, 1946, and a stenosing endobronchial disease, left main stem bronchus, since July, 1945. Multiple cavitary lesions were present. Her general condition was good, and pneumonectomy and thoracoplasty were recommended. These procedures were carried out in December, 1949, and January, 1950. Marked improvement has followed operation (figures 9 and 10).

Case 7. A 36 year old white male had had proved moderately advanced pulmonary tuberculosis since August, 1946, which had been treated by artificial pneumothorax for two years. Therapy was complicated by unexpandable pneumothorax and persistent fibrocavernous lesion, right upper lobe. The patient was admitted to Fitzsimons August 23, 1948. Lobectomy, right upper lobe, and thoracoplasty, five ribs, were completed December 21. The surgical specimen demonstrated cavitation, caseous foci and acid-fast bacilli.

This patient exemplifies the problem of active pulmonary tuberculosis complicated by an unexpandable, unsatisfactory pneumothorax. The pulmonary lesion is classified as an old fibrocavernous lesion (figures 11 and 12). The control of the pulmonary disease is one of the prerequisites to decortication for an unexpandable pneumothorax. In this case, the problem was solved by removal of the diseased lobe, decortication of the remaining lung tissue and a five-rib thoracoplasty to decrease the danger of reactivating latent foci. The obvious advantage of a small thoracoplasty and excision of the diseased tissue with a good cosmetic result, over a more extensive thoracoplasty with less chance of success, is well demonstrated in this case.

Summary

Prior to 1945, the early or late mortality rate was one out of every four patients on whom lobectomy was performed for pulmonary tuberculosis, with major complications of spread or reactivation of the disease postoperatively variously reported as from 20 to 60 per cent, empyema, 15 to 25 per cent, and bronchopleural fistula, 15 to 20 per cent. However, we have emerged from this dismal picture with much more gratifying results. In our recent experience, beginning in 1947 with 94 consecutive patients on whom lobectomy has been performed for pulmonary tuberculosis, we have had two deaths, early or late, a mortality of 2.12 per cent. Reactivation or spread of the disease has occurred in five patients, empyema in two and bronchopleural fistulae in five. In an overall summary of 124 patients on whom pulmonary excision has been performed for the treatment of pulmonary tuberculosis, including pneumonectomy, segmental or partial resection of a lobe, or total lobectomy, the overall mortality rate, both early and late, has been 4 per cent. These striking improvements are attributable not to any one factor but rather to several developments; however, the common denominator not previously available has been streptomycin. We believe this antibiotic, and more recently combined therapy with para-aminosalicylic acid, have been the most important factors in the recent improvement of pulmonary resection in tuberculosis. Final evaluation must await the experience of a long term follow-up study.

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MILITARY PSYCHIATRY TODAY*

By Francis J. Braceland, M.D., F.A.C.P., *Rochester, Minnesota*

> The thing that hath been, it is that which shall be; and that which is done is that which shall be done: and there is no new thing under the sun. Ecclesiastes 1:9.

Five years ago, in a report issued at the close of World War II, the present writer stated "Each successive war brings with it new problems, but the old ones crop up repeatedly and as we encounter them again and again we wonder why man is so slow to profit by experience and history. Perhaps the cynic expressed it best of all when he said 'Men learn from history only that men learn nothing from history.' To this we might add Santayana's remark that those who cannot remember the past are condemned to repeat it."

Today, as the armed forces once again undergo partial mobilization, there is a chance that these criticisms may be avoided and that we really have learned from history. The military services for the first time are possessed of a cadre of experienced psychiatrists in key positions, who have the essential "know how," who are cognizant of past experiences and who are capable of imparting their knowledge of administrative and combat psychiatry to younger officers.

There are two aspects to the problems which confront the military psychiatrist today. The first we may call the "symptomatic"; the second we can designate the "etiologic," although neither of these terms is quite descriptive enough. By the "symptomatic" aspects of the problems we mean those aspects which lie in the realm of more efficient technics with which to treat the symptoms which bring the patient to the psychiatrist's attention. In the military services, for example, the psychiatrist most frequently is concerned with the various manifestations of anxiety and the defenses which people erect against their anxiety. Fortunately, lessons learned in World Wars I and II throw a great deal of light upon various problems which the military psychiatrist encounters, and a large body of data has been assembled with which the findings of the specialists who worked in the field can be documented. Specifically, these data concern the problems of selection and screening methods, methods of training, the important rôle of leadership, and group affiliation, as well as physiologic, pharmacologic and psychologic methods of moderating the severity of the stress which military personnel encounter. In a general way, I refer to the judicious use of sedation, narco-analysis, narcosynthesis, shock therapy and the various methods of treatment which go to make up the therapeutic armamentarium of the psychiatrist.

*Read at the 32nd Annual Session of the American College of Physicians, St. Louis, Missouri, April 10, 1951.

There are numerous truths which have been discovered and rediscovered by observations of the behavior of men in combat, and some of these, indeed, are self-evident. It would be supererogatory to note here that fresh, well-trained and seasoned troops have higher thresholds of resistance to the inroads of psychologic stress than do unprepared, fatigued and wounded men. The fact that psychiatric casualties are best treated in forward areas and away from the hospital atmosphere is also something that we rediscover periodically. The governors of the Government Hospital for the Insane told us in 1863 that unless we selected men with "the mental vigor and endurance necessary to receive and practice the discipline of a soldier he will involuntarily betray both his companions and his country in the hour of battle, the hour of his supreme trial and render worse than useless a costly novitiate." Thomas Salmon and his colleagues, who wrote volume 10 of the *Medical History of World War I*, described in detail the problem of shell shock, as did Dr. George Burr, writing in the *New York Medical Journal* for September, 1865. General Menninger, Captain Kennedy, Colonel John Murray and their associates and colleagues added to the knowledge handed down to us, and their publications summarize the military psychiatric experiences of World War II.

More recently, Colonel Fred. Hanson and his colleagues, writing in a supplemental number of the *Bulletin of the Armed Forces Medical Department*, entitled "Combat Psychiatry," summarized the results of their experiences of two and a half years under nearly all kinds of combat conditions. Essentially, then, we should have insight into the vicissitudes of military life, for they have been pointed out by military writers since the time of Thucydides. Fortunately, the trained cadre of psychiatrists mentioned above as being in key positions will constitute a large and dependable buffer against the necessity of having to learn this laboriously all over again.

Undoubtedly, the present emergency and the newer weapons and different terrain will impose their own unique hazards upon the picture. Ingenuity will again be taxed, but it is certain that the necessary change in operational devices will be brought about. An example of a new problem which will be encountered is the zeal of evacuation officers to clear area beds of neuropsychiatric casualties via the new and very efficient system of air transportation. The psychiatrist will have to maintain an efficient liaison with these officers lest his patients get quick rides or a hitch hike to a psychiatric "Blighty."

In a larger sense, it is at once apparent that what we have called the "symptomatic" treatment of psychiatric disorders, essential as it is, might be compared in the vernacular to bailing out the boat rather than caulking the seams. Every great advance in medicine has followed a shift in perspective from symptoms to causes. By the same token, the real advances in military psychiatry, which we all eagerly await, will come when not only psychiatrists but all persons recognize that forces collectively called "motivation" and

"morale" are the most important psychologic elements of military life. We have given lip service to this idea at regular intervals, but have never actually used it as it should be used. What makes a soldier fight? What keeps him fighting? What are the elements which turn him from his job of fighting? A great step forward was made in modern medicine when due recognition was given to the fact that mind and body, physiology and psychology, operate congruently. New understandings were ours as a result of this. Now we find that we need not only be concerned with the mind and body, but also with the social milieu in which these actions take place. To those of us who are inclined to shudder at having now to consider the sociologic aspects of the problem, having just recently accepted the psychosomatic, I would say: We as physicians have the resulting problems to treat. If we have them passed on to us, it behooves us to look into their etiology and it is this etiology which I should like to consider with you. It is the problem of means and ends, and of individuals and of groups of individuals, for this has a direct bearing upon military psychiatry today.

When we consider the ingredients of motivation in an attempt to assess the psychologic problems which confront the nation as a whole, and that part of it which makes up the armed forces, we must ask the question: "What are we fighting for?" True enough, we really know: it is the distance of the scene of action which seems to be the difficult psychologic gap for us to bridge. War as a distant threat or reality is an unpleasantness to be shunned and avoided—a realization to be repressed, in psychiatric terms. Added to this, as we are knee-deep in the present emergency, there are violent differences of opinion as to ways and means, reasons for and against, each of our important military and domestic problems which will influence the life of the nation. Each side has sincere, capable, and distinguished individuals as proponents. The bearing all this has upon the morale of troops is considerable, for although political issues at home at first glance seem far removed from military tactics in the field and day-to-day fighting, Von Clausewitz pointed out that war is merely an instrumentality of politics, and therefore we, while members of the armed forces, are instruments by which the faiths and beliefs of our government are expressed. Lack of unanimity of political strategy and tactics points up another historical lesson we learned in World War II. We live in a tightly organized society. Currents and problems in one realm have beneficial or deleterious effects upon all other component parts. What happened in Munich affected people here; what happens in Seoul affects the lives and fortunes of each one of us. Consequently it is not going far afield to consider the influence of these social and political currents upon the lives of soldiers and sailors.

World War II taught us many lessons in psychologic warfare. Psychologic warfare means not only what we do to an enemy; it is also what an enemy does to us. Consideration of social forces is an inquiry into the weapons of psychologic warfare. That ideas are weapons is not a new

concept. That conflicts in ideas provoke anxiety is also well known. That anxiety is the nuclear problem the military psychiatrist treats is self-evident truth. Consequently, ideas, political and social, have much to do with the stability of the soldier and sailor.

Now it is patent that in a democracy no clear-cut answers can be readily given to the complicated problems which face us. Only totalitarian societies have the dubious advantage of absolute opinions. By the same token, it is incumbent upon us to train our youth to accept conflict as something inherent in a democratic process and particularly in issues of such magnitude as those which face us today. As victors, we would be vanquished if we were to win because no differences of opinion were allowed in order to avoid conflict.

All of us need to learn to accept the fact of conflict without being seriously affected. Conflict in Germany, Poland or in the Politburo is not allowed—there it is bad. Anxiety of itself is not bad—the psychiatrist does not seek to remove the normal anxiety: he seeks to channel it. Fever of itself is not bad; it is a symptom and it has its uses. Similarly, then, conflict when searching and well reasoned can be salutary. To train youth to this, one has to teach them to ask questions and to instruct them beyond the knowledge of technics alone. It takes them into the realm of morality and ethics. A senator recently took cognizance of this in an address which attracted national attention. It was the gist of his thesis that our nation is more likely to be destroyed by the abandonment of our true moral principles than by armed attack from the enemy.

One historical lesson which modern psychiatry has learned well is that attitudes and values determine psychologic stability and increase or limit the capacity of an individual to adapt to stress. The symptoms of stress in the body politic are homologues of the anxieties, dissatisfactions and behavioral disturbances which the military psychiatrist treats in his practice. Unless we as physicians and all of us as citizens recognize and accept our responsibility in the over-all training of our young people, we shall continue to create more psychiatric problems than a division of psychiatrists or many divisions of psychiatrists could treat. The answer lies not in better psychiatric technics, for important and necessary as they are when we need them, the mere fact that they have been devised means that some damage has already been done. Psychiatrists, like their colleagues in other branches of medicine, are mindful of the essentiality of preventive medicine, and this is preventive psychologic medicine. Preventive psychiatry is not solely the responsibility of military psychiatrists or civilian psychiatrists—it extends even far beyond the purview of medicine and involves the nation collectively.

There are problems now agitating the nation; namely, the so-called teenage draft and universal military training. These are old problems, too. Surgeon General of the Army Hammond had some pretty strong but undocumented opinions about it which he expressed in his report in 1862.

From the standpoint of the psychiatrist, it is a specious argument as to whether drafting the 18-year-old or 18½-year-old is likely to produce more stress. We have need to approach this problem as we would our civilian defense and our over-all political way of life. An informed citizenry is the best bulwark against the corrosive inroads of psychologic insecurity, whether it be cold war or hot war. Ideas are the weapons for this type of preparation. Whether the man be 18, 18½ or 22 years old, his way of life is a job not limited by chronology. Military and political issues will determine which class we must call up when the members thereof will be needed.

Lessons of World Wars I and II are quite clear and emphatic in regard to the immunizing effect of training and over-all preparation for the stress of combat. The job of the military psychiatrist will be immeasurably lightened if the significance of this fact is constantly kept in mind. Unprepared and unseasoned troops placed in jerry-built outfits unacquainted with the job and with one another are fertile soil in which high neuropsychiatric casualty rates will grow.

The time for training is not alone that which takes place in the military services when the boy is in uniform. It begins in the home, in the school and in the daily activities. It answers the question as to why we fight, and gives the boy something he can believe with conviction. To enable such boys to find a proper sense of values and a realization of responsibility and belongingness is strong protection against the possibility of their becoming neuropsychiatric casualties.

None of this, of course, negates the importance of individual susceptibility to the inroads of emotional stress nor does it forget that the reason for war neuroses is war. These things are recognized and given proper importance. It simply calls attention to the strengthening effect of proper morale and motivation. The people of London and of other cities which were under fire and bombing did not become neuropsychiatric casualties, even in the numbers expected. In fact, the neuropsychiatric clinics generally noted a decline in attendance. Each one of us knows of individuals and groups of individuals who, while having difficulty in civilian life from an emotional standpoint, distinguished themselves in the service. They were properly imbued and properly motivated.

There are, of course, many of what we have called the "symptomatic" aspects of the problem, which still need attention. They will be managed and investigated this time by a larger group of psychiatrists who on the whole are better trained. You will find them chastened by the past decade, which has been a productive one, and inasmuch as they and what they have to teach will meet with much better reception and understanding, the prospects are much better for a broader and more efficient military psychiatry today.

CASE REPORTS

RUPTURED ANEURYSM OF THE SPLENIC ARTERY: CASE REPORT WITH DISCUSSION *

By GEORGE W. ZELUFF, M.D., *Houston, Texas,* and VICTOR PARSONNET, M.D., *Valhalla, New York*

RUPTURE of an aneurysm of the splenic artery is a rare cause of acute blood loss. If such a diagnosis is borne in mind, it is possible to cure the patient by means of surgical intervention. This case is of interest because ample time was available for surgery if the diagnosis had been made, and because of the unusual site of rupture.

CASE REPORT

The patient, a 32 year old housewife, was admitted for the first time on October 21, 1947, with a diagnosis of pleural effusion that had been made by her physician. The past and personal histories were essentially noncontributory. She had never been pregnant, and there was no history of pulmonary disease, renal disease or hypertension. Five weeks prior to hospitalization she noted a constant dull pain in the left anterior chest not related to exertion or respiration. This was accompanied by vague malaise, swelling of her abdomen and inconstant low back pain. A physician administered oral penicillin without appreciable response. Three weeks prior to admission she noted exertional dyspnea and orthopnea, followed by a further increase of the size of her abdomen. Thoracentesis of the left chest by her physician yielded about a quart of brown fluid. When this fluid re-accumulated over a period of a few days she was sent to the hospital. The patient denied cough and hemoptysis. Stools were said to be normal. A weight gain of 8 pounds was noted in the two weeks before admission.

Physical Examination: The patient was a thin, pale young white woman, who was dyspneic and orthopneic, with a temperature of 101° F., pulse 106, respirations 36, and blood pressure 138 mm. Hg systolic and 106 mm. diastolic. Repeated blood pressure determinations were within normal limits (124/80, 130/84). Positive findings included signs of a massive pleural effusion in the left chest with a shift of the mediastinum to the right, a distended, tympanitic abdomen with questionable signs of fluid, and a firm, slightly tender mass in the left upper quadrant, extending 6 cm. below the costal margin, that was believed to be the spleen. A smooth, firm, nontender liver edge was palpated 3 cm. below the costal margin. Pitting edema of the legs, feet and sacrum was present. The heart and the right lung were normal. Pelvic, rectal and neurologic examinations were within normal limits.

Course: After an initial week of fever, the patient remained essentially afebrile. The left chest was repeatedly tapped, and a total of 9,400 c.c. of fluid was removed. This fluid was always a dark red-brown in appearance and contained many red blood cells and no neoplastic cells; it was sterile on repeated cultures. Anemia, present

* Received for publication June 9, 1949.
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on admission, progressed in severity to a level of 8 gm. of hemoglobin. The spleen increased in size, reaching the umbilicus. Many diagnostic procedures were done, including gynecologic studies, cystoscopy and retrograde pyelography, all of which were normal. Roentgenograms revealed the left pleural effusion (figure 1), mediastinal shift and normal excretory urography. Irregular calcified nodules, thought to be in the pancreas, were noted. No lesions were found in the colon, stomach or duodenum. The stomach was displaced forward and to the right by a mass interpreted as either spleen or a cyst of the body or tail of the pancreas (figure 2).

Repeated urinalyses were negative except for an occasional specimen with several red blood cells. The white blood count remained normal. The sedimentation rate

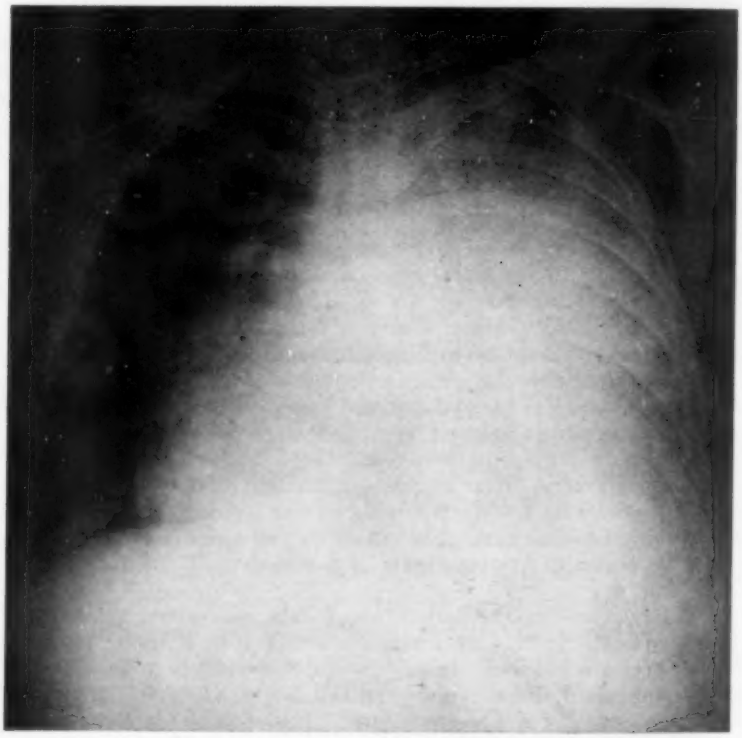

FIG. 1. Roentgenogram of chest. The mediastinum is shifted toward the right and there is a left hemothorax.

was constantly elevated at levels around 60 mm. per hour. Several stools were negative for blood. Blood urea nitrogen, icterus index, serum proteins, alkaline phosphatase, phosphorus, cholesterol and the cephalin-cholesterol flocculation test were within normal limits. The Wassermann test was negative, as were enteric agglutination tests and several blood cultures. No abnormal bleeding tendency was found, with the bleeding, clotting and prothrombin times within normal range.

On the fifty-fourth hospital day, the patient refused a sternal marrow puncture and signed out of the hospital at her own request.

The second admission occurred 11 days later, when the patient complained of dyspnea and severe pain in her left chest. Shortly after being sent to the ward, she

suddenly sat upright on the stretcher, screamed loudly and complained of generalized chest pain; she then collapsed, became cyanotic and died a few minutes later. Her death occurred 100 days after the onset of her illness. No clinical diagnosis was made.

Necropsy: Only the pertinent findings are presented. The heart weighed 220 gm. and was without lesions. There was no gross abnormality of the aorta; no atherosclerotic plaques were seen. Histologic examination of the aorta revealed necrosis of the smooth muscle fibers of the media, most marked in the inner half, with accumulation of mucoid material between the lamellae, and formation of small cysts. The

FIG. 2. Roentgenogram of upper gastrointestinal tract. The mass is pressing on the greater curvature of the stomach.

mucoid character of the material was confirmed by Mayer's mucicarmine stain. The intima and adventitia appeared normal. Weigert's elastic tissue-Van Gieson stains disclosed spreading of the elastic lamellae by the cysts, and slight fragmentation of the elastica of the media.

The left pleural and peritoneal cavities were filled with fresh and old clotted blood. One centimeter from the origin of the splenic artery, and extending 2.5 cm. along it, was a saccular aneurysm. Distal to the aneurysm the splenic artery resumed its normal size. Both the splenic artery and the vein were patent throughout. The aneurysmal sac measured 10 cm. in diameter and was filled with old and freshly clotted blood. Many outpouches of varying size arose from it; one of these extended

along the proximal portion of the splenic artery to a point beneath the posterior surface of the right leaf of the diaphragm. Several of these reached the left leaf of the diaphragm, one of which was adherent to and had extended through the diaphragm and ruptured into the left pleural cavity. Blood had also escaped into the peritoneal cavity.

Histologic examination of the aneurysmal sac revealed the wall to be composed of dense layers of fibrous tissue in which were small blood vessels; some of these were surrounded by cuffs of lymphocytes. No elastic tissue could be demonstrated in the wall of the aneurysm. Sections of the splenic artery distal to the aneurysm showed a few foci of mucinous change in the media. The elastic tissue of the media was normal. This process was extremely mild in the portion of the splenic artery sectioned.

The aneurysm pressed on the midportion of the pancreas. Distal to the aneurysmal mass the pancreas was atrophic and the duct dilated. There were many small white calculi partially occluding the ducts of the pancreas, both proximal and distal to the aneurysm. Histologically there was extensive disappearance of pancreatic acini, with dilatation of the intralobular ducts and extensive interlobular and intralobular fibrosis. The interlobular ducts were dilated. The islets were normal.

The spleen was enlarged, weighing 300 gm., and was acutely congested. There was no evidence of infarction. In view of the patency of the splenic artery and vein, the only possible explanation for the congestion was compression of the lumen of the vein by the aneurysm.

No arteriolarsclerosis or congenital malformations were found in any of the viscera.

Anatomic Diagnosis: Aneurysm of the splenic artery with rupture; medial necrosis of the aorta; pancreatic calculi; fibrosis of pancreas.

Discussion

The incidence of splenic artery aneurysm has been varyingly reported as from one in 1,150 [1] autopsies to one in 3,360.[2] Cosgrove [2] collected a series of 98 cases in which there were 60 females and 38 males. The average age was 48 years. A higher percentage of females was found in the younger age groups, with no preponderant sex distribution after the age of 45.[3] Of 60 females, 15 were pregnant, a finding which was repeatedly reported in the literature.[3, 4, 5, 6, 7, 8] No adequate explanation for the frequent occurrence of splenic aneurysm during pregnancy has been given.

Multiple factors may be responsible for the formation of splenic artery aneurysms. Most frequent among these factors are arteriosclerosis, septic emboli and congenital anomalies.[9] The former is prominent in the old age groups. Occasionally trauma,[10] "wandering spleen," Gaucher's disease, Banti's disease,[2] syphilis [11] and medial necrosis [6, 14] have been cited in association with splenic aneurysm. In the case reported here, all of these possibilities are excluded except congenital anomaly and medial necrosis.

Forbus [12] studied miliary aneurysms of the cerebral arteries and demonstrated a muscular defect in the media located in the portion of the vessel wall at the angle of bifurcation. A similar medial defect was found in other arteries, including coronary and mesenteric, as well as in arteries with aneurysmal dilatations. The muscularis of an artery develops from a group of mesenchymal cells quite distinct from those which form the muscularis of the branches of the vessel, and the muscularis of the parent vessel develops earlier than that of its branches. A failure

of the two separately developing muscle coats to fuse properly may offer an explanation for the defect observed in the mature artery.

In favor of the hypothesis that this underlying mechanism accounts for later aneurysm formation at the point of bifurcation is the fact that miliary aneurysms usually occupy the angle formed by a branching artery.[2, 12] Also, the muscularis defect, a "locus minoris resistentiae," is found at the point of bifurcation where, as has been shown experimentally, there is maximum pressure on the vessel wall.[12] On this basis, Forbus concluded that miliary aneurysms of arteries of medium size occur independently of any inflammatory process, arteriosclerosis or trauma, and, as such, are not congenital malformations; they are acquired lesions resulting from a combination of focal weakness in the vessel wall, due to a congenital muscular defect, and degeneration of the internal elastic membrane from continual overstretching. Confirmation of this concept was offered in a case described by Nevin [13] with fatal rupture of a splenic artery aneurysm into the peritoneal cavity. The splenic artery aneurysm, as well as four cerebral aneurysms that were found incidentally, showed the characteristic medial defect as described by Forbus.

In view of the fact that increased intraarterial pressure at the site of this developmental defect may lead to aneurysm formation,[12] it is interesting to note the high incidence of splenic artery aneurysms in pregnant women. The increased intravascular pressure due to the large abdominal mass, increased blood volume and mild hypertension, together with the secondary hormonal dilatation of the smaller arteries, may offer a possible explanation for this high incidence during pregnancy.

An additional etiologic factor to be considered in the evolution of aneurysms of medium-sized arteries is the presence of medial necrosis. Little has been written concerning the rôle of medial necrosis in the formation of splenic artery aneurysms, although this factor has been suggested.[6, 14] Bauer and Apfelbach [6] reported a case of a ruptured splenic artery aneurysm in a pregnant woman; they described a "degeneration of the media limited entirely to branches of the coeliac axis." The histologic alterations were an "excessive retrogressive change, vacuolization, and atrophy of the media," together with masses in the media which took a blue stain. Anderson and Gray [14] also reported a case of a ruptured splenic artery aneurysm in a 49 year old woman in which "medial degeneration and necrosis were the primary and chief factors leading to the formation of the aneurysm."

The rôle of medial necrosis, or "medionecrosis aortae idiopathica cystica," as described by Erdheim,[15] has been discussed in the formation of aortic aneurysms.[16, 17] Tyson [18] suggested that the medial necrosis is secondary to either a low grade inflammatory reaction or sclerosis of the vasa vasorum. Rottino [16] believed that the weakening of the wall produced by these changes can lead to aneurysmal dilatation grossly indistinguishable from luetic dilatation. Extensive fibrosis of an aneurysm wall would not be against such an etiology, since repair by fibrosis may be the last stage of this process.[19]

Possibly the etiology of the aneurysm in this patient was medial necrosis, although only fibrosis was seen in the aneurysm wall. The lesion in the aorta is similar to that described by Erdheim [15] and Rottino.[16] Congenital anomaly as an etiologic factor is unlikely, because the aneurysm was not located at a point of branching, and because no other aneurysms or congenital anomalies were found.

The symptomatology of splenic artery aneurysms is extremely variable, and is often nonexistent until encroachment upon other structures is evident [9] or

rupture occurs. In the series of 63 cases collected by Cosgrove,[2] 25 had varying symptoms of a chronic nature with a long history of upper abdominal pain, vomiting, vague gastrointestinal complaints, weight loss, anemia, changes in bowel habits, dyspnea and syncope. Occasionally the first evidence was the discovery of a mass, otherwise symptomless, by the patient.[20] The intensified symptoms and signs were usually related to rupture; these were sudden severe abdominal pain, melena and hematemesis, when rupture occurred into the gastrointestinal tract, apprehension, dyspnea, syncope, vomiting, shoulder pain, urge for defecation, prostration, low blood pressure, and other signs of shock and rapid blood loss. Physical findings of importance included the presence of an abdominal mass in 13 of the 63 cases, splenomegaly in 22, localized pulsation in five, and bruit in five. The importance of applying a stethoscope to the abdomen [8] in abdominal tumors was emphasized by Farrell,[21] who made the diagnosis on the basis of a bruit and operated successfully.

Certain laboratory data may aid in the diagnosis. The finding of steatorrhea, probably due to obstruction of the pancreatic duct, is an unusual but helpful feature.[8, 21] Roentgen-ray examination may reveal pancreatic calculi, as in this patient, calcification in the wall of the aneurysm,[22, 23] or filling defects in the stomach. The latter have been reported on the lesser [8] and greater [5] curvatures. These defects may pulsate when observed under the fluoroscope.

The aneurysm may rupture in one of two ways: the rupture may be sudden, with rapidly fatal blood loss, or it may be in stages.[4, 24] The latter may be prolonged from several hours to months, the terminal episode being one of rapid hemorrhage. An explanation for the rupture in stages has been offered by Machemer,[9] who states that there may be slow fissuring of the aneurysmal sac with formation of a surrounding hematoma. The hematoma becomes organized and is surrounded by fibrous adhesions. Subsequent rupture into this mass of adhesions tends to limit the extent of the hemorrhage. Presumably, in the case reported here, there must be adhesions between the aneurysm and the diaphragm, with subsequent degeneration of the latter by pressure necrosis.

The site of the rupture is varied. According to Cosgrove, the sites are in descending order of frequency: peritoneal cavity, retroperitoneal tissue, stomach, colon, pancreas, and combinations thereof. As far as we have been able to determine, no previous case has been reported of rupture into the thoracic cavity.

It is doubtful whether steatorrhea was present in this patient, because the first portion of the pancreas was unaltered. Calculi were formed, probably from inspissated material trapped in the obstructed ducts.

Treatment consists of combating shock, and of general supportive measures and surgery. Tamponade is ineffective.[21, 25] Simple ligation of the splenic artery proximal to the aneurysm has been performed successfully,[26] the spleen undergoing aseptic necrosis. Ligation of the splenic artery has also been done without untoward effect in animals.[21] The ideal procedure is complete removal of the aneurysmal sac and spleen, preferably prior to rupture if the diagnosis is made.[10, 20, 21, 24, 27]

Summary

1. An unusual case of rupture of an aneurysm of the splenic artery into the thoracic cavity is presented.

2. It is important to bear this condition in mind because of the possibility of cure through surgical intervention.

3. Important diagnostic aids are the signs of an upper abdominal mass with a bruit, steatorrhea, and roentgen-ray evidence of calcification in the aneurysm, pancreatic calculi or pulsating gastric filling defects.

4. The incidence, etiology and pathology are discussed.

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RENAL FUNCTION STUDIES IN ACUTE SYPHILITIC NEPHROSIS BEFORE AND AFTER TREATMENT WITH PENICILLIN * †

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SYPHILIS of the kidney includes a variety of renal lesions, none of which is well defined pathologically. The most common of these conditions, with the exception of slight and uncomplicated albuminuria unassociated with any other evidence of nephropathy, is the so-called acute syphilitic nephrosis. This type of nephritis may appear during the acute (secondary and probably late primary) phase of the infection. The incidence is less than 1 per cent in cases of secondary syphilis.[4] In 1935 Hermann and Marr [12] reviewed comprehensively the general subject of syphilitic nephropathies, and found eight unequivocal and four probable (data incomplete) cases of acute syphilitic nephrosis. They added one case of this type from their own experience. Since then reports of 22 additional cases [1, 2, 3, 4, 5, 6, 7, 9, 10] have appeared in the American literature.

Although antiluetic treatment was administered to most of these cases, spontaneous subsidence of acute nephrosis prior to antiluetic therapy has been reported by Patton and Corlette [3] from this clinic. Nephrosis has also appeared as a Herxheimer phenomenon in uncomplicated secondary syphilis following treatment with arsenicals and also penicillin.[11] To date, nine cases have been treated with penicillin.[1, 2, 4, 5, 9, 10, 11]

Little is known concerning the anatomic or physiologic pathology of syphilitic nephrosis. Direct examination of the kidneys in the acute phase of this disease has not been reported. Acute nephrosis in experimental syphilis has not been observed.[8]

The clinical picture consists of generalized edema and varying degrees of oliguria. Subjectively, there is little or nothing to indicate illness. The patient appears well or only mildly ill. In addition to the edema there may be evidence of syphilis in the form of a rash, mucous membrane lesions or a healed primary lesion. Not infrequently there is local or general lymph node enlargement. The benign clinical picture may aid in distinguishing this nephropathy from acute glomerular nephritis which might complicate acute syphilis. However, the laboratory findings are of major value in establishing the diagnosis. The blood Wassermann reaction is strongly positive. There is heavy proteinuria with cylindruria (usually hyaline or granular casts, occasionally white cell casts). The urine also contains white blood cells and, less commonly, red blood cells. Tests of renal function, including phenolsulfonphthalein excretion, urea clearance and concentration tests, show little or no impairment. There is no elevation of the

* Received for publication February 8, 1950.

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† This study was supported in part by grants-in-aid from the U.S.P.H.S., Eli Lilly and Company and Ciba Pharmaceutical Products, Inc.

§ Work done during the tenure of a National Research Council Fellowship.

blood non-protein-nitrogen. The serum cholesterol is usually elevated, the total serum protein value is frequently low, and reversal of the albumin-globulin ratio is common. The basal metabolic rate is usually at a normal or low normal value. The finding of doubly-refractile bodies in the urine seems to be the exception rather than the rule. Rapid diuresis and cessation of proteinuria following antiluetic therapy are characteristic of syphilitic nephrosis. The other clinical abnormalities return to normal somewhat less rapidly.

Recently we had the opportunity to study renal plasma flow, glomerular filtration rate and maximum tubular excretion in a patient with syphilitic nephrosis. The results of these studies are set down here. We believe they represent the first observations of this nature in acute syphilitic nephrosis.

Case Report

An 18 year old colored male entered Vanderbilt University Hospital on February 15, 1948, with a chief complaint of "swelling of the ankles." Three weeks prior to admission he had experienced a mild sore throat and coryza associated with moderate malaise and anorexia. After about one week he felt better but noticed tender swelling of the postauricular lymph nodes bilaterally. Mild coryza and anorexia persisted, and during the second week he felt feverish on occasions and transient spells of dizziness and blurring of vision occurred. Sore throat recurred, and for three days he experienced watery diarrhea. There were 10 to 12 watery stools per day, some containing streaks of blood. The diarrhea was terminated by paregoric. The patient continued in school during this illness except during the period of diarrhea. The enlarged postauricular lymph nodes subsided, but four days before admission he noted a large tender node in the submental region. It was at about this time that he noticed edema of the face and ankles. He voided frequently but there were no other urinary symptoms. He denied any rash.

Past History: Birth and development had been normal. He had had measles and mumps as a child. In March of 1946, at age 16, he contracted gonorrhea which was treated successfully with oral sulfathiazole. There was no history of scarlet fever, frequent sore throats, rheumatic fever, chorea, diphtheria, malaria, anemia or tuberculosis. A tonsillectomy had been performed at age seven. He gave a history of "hay fever" occurring in late summer. There was no other history of allergy.

Family History: This was noncontributory. Each parent was subsequently found to have a negative serologic test for syphilis.

Physical Examination: On admission, the temperature was 98.2° F.; pulse 80; respirations 20, and blood pressure 120 mm. Hg systolic and 70 mm. diastolic.

The patient was well developed. He was in no distress. There was facial edema of moderate degree, most marked in the periorbital region. The skin was warm and smooth. There was some fine, dry scaling of the skin over the abdomen and flanks, but no rash was noted here or elsewhere. The mucous membranes were normal. There was generalized lymph node enlargement with a large, tender, firm submental node about 1.5 centimeters in diameter. The eyes were normal. The nose, ears and mouth were normal. There was slight edema of the pharyngeal mucosa. The neck was supple, the thyroid normal. The lungs were clear. The heart was not enlarged. There was a regular sinus rhythm and the sounds were of good quality. There were no murmurs. The abdomen was scaphoid, and no viscera, masses or tenderness were made out. The genitalia were those of a normal male. There was no evidence of scar or other lesion. There was no urethral discharge. The rectal examination was not remarkable. The prostate was of normal size and consistency. The extremities were not remarkable except for a 2 plus pitting edema which extended up to the knees. Joints were normal. Reflexes physiologic.

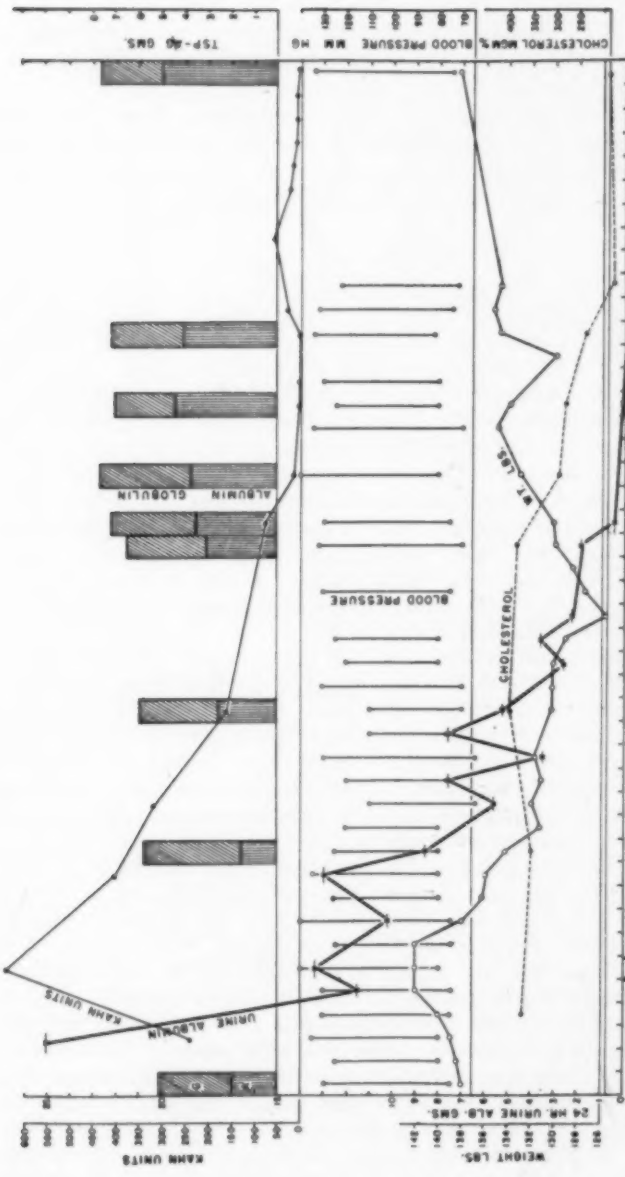

FIG. 1. Graph showing Kahn titer, total serum proteins and albumin globulin values, 24 hour urine albumin content, blood pressure, body weight and serum cholesterol values. Along the abscissa are indicated the dates of penicillin administration and renal blood flow studies.

Course in Hospital: (See figure.) The day of admission (February 15, 1948), the urine showed a specific gravity of 1.045, 4 plus albumin, pH 6, with numerous fine granular and red cell casts, six to eight red blood cells and two to four white blood cells per high power field. The red count was 4.16 million, hemoglobin 12.5 gm., 5,400 leukocytes with 59 per cent segs., 30 per cent lymphocytes, 3 per cent monocytes, 2 per cent basophils, 5 per cent eosinophils and 1 per cent stabs. This was the basic leukocyte pattern throughout the period of hospitalization. The erythrocyte sedimentation rate ranged from the upper limits of normal to 40 mm. per hour (Wintrobe). The blood Wassermann and Kahn reactions were positive. The total serum protein was 5.16 gm. per cent with a reversal of the A/G ratio. The cholesterol value on the third hospital day was 370 mg. per cent, and this subsequently became elevated as high as 404. The non-protein-nitrogen value varied between 23 and 35 mg. per cent on seven occasions. A phenolsulfonphthalein test showed normal excretion. He was given a low sodium diet. It seemed apparent that this patient was suffering from some form of nephrosis, and the positive serologic test for syphilis suggested the possibility of syphilitic nephrosis. On the fifth hospital day a Kahn titer of 640 units was reported. At this time a single ulcer, firm to the touch, was discovered in the mouth on the buccal mucosa. It yielded *Treponema pallidum* on dark field examination. This left no doubt that we were dealing with syphilis complicated by nephrosis.

On the morning of the fifth hospital day renal clearance studies were carried out and, following these studies, treatment was begun with penicillin. The patient received 40,000 units every three hours for 120 doses, or a total of 4.8 million units. On the third hospital day the patient began to have a low-grade fever of 99 to 100.4° F., which continued for nine days, the latter seven of which were during the period of penicillin treatment. The admission weight had risen to 142 pounds because of edema. The blood pressure remained within normal limits during the entire period of observation.

During the course of penicillin therapy the weight began to fall, and for a few days urinary output exceeded fluid intake. At the time of discharge on the twenty-second hospital day the weight was only 129, a loss of 13 pounds from the maximum of 142 pounds. The patient was free of edema; however, the serum cholesterol was still elevated, in the range of 380 to 400 mg. per cent. The Kahn titer began to fall shortly after penicillin was started and, at discharge, was approximately 125 units. The total serum proteins rose steadily to a normal value. The albumin fraction was chiefly responsible for this rise, so that the normal A/G ratio was soon reëstablished. Albuminuria diminished and the urine was free from albumin three days after penicillin was discontinued. After discharge the patient was followed carefully. The Kahn titer fell to a low of 4 units on the forty-seventh day after the completion of therapy. By this time the cholesterol had fallen to 280 mg. per cent. His weight had risen somewhat, but this appeared to be an actual gain in flesh. There was no evidence of edema.

On March 7, April 14 and May 25, 1948, renal clearance studies were again carried out. These dates represent the day following the completion of penicillin therapy and the thirty-ninth and eightieth days, respectively. These results are tabulated in the accompanying table. On June 11, 1948, approximately three months after discharge, the Kahn titer was 4 units. The total serum protein value was 7.12 gm., with a normal A/G ratio. The Wassermann reaction was negative. The cholesterol and non-protein-nitrogen values were normal. On July 22, 1948, six weeks after discharge, the Wassermann test was again positive and the Kahn titer had risen to 30 units. Six weeks later the titer was 40 units. There were no urinary abnormalities and no evidence of recurrence of the nephrosis. The non-protein-nitrogen and cholesterol values remained normal. In view of this serologic relapse the patient was

TABLE OF CLEARANCE VALUES

DATE	2-20-48	3-7-48	4-14-48	5-25-48	NORMAL
METHOD	STANDARD	STANDARD	STANDARD	SIMPLIFIED	VALUES *
R.P.F. cc/min.	456	525	498	494	697±136 cc/min. (13)
G.F.R. cc/min.	76.1	106.5	121	152	131±21.5 cc/min. (13)
FILTRATION FRACTION (%)	16.7	20.3	24.3	30.8	19±2% (13)
TM_{PAH} mgm/min.	49.8	77.0	67.7	—	77.5±12.9 mgm/min. (18)
C_{PAH}/TM_{PAH}	9.16	6.8	7.36	—	9.0
C_{IN}/TM_{PAH}	1.53	1.38	1.79	—	1.7

* Smith's [13] values for R.P.F. and G.F.R. quoted here were derived from simultaneous measurements of at least three diodrast and inulin clearances in each of 61 normal males. These values may be compared with 621 ± 133 c.c./min. for R.P.F. and 112 ± 15.5 c.c./min. for G.F.R. derived by Chasis et al.[18] from simultaneous measurements of single clearance periods of p-aminohippurate and inulin in 19 normal males and females. The value for TM_{PAH} is that reported by Chasis [18] and is derived from observations on a mixed group of 31 normal subjects, using both single and multiple period technics. It agrees well with the value 76.1 mg./min. reported by Goldring and Chasis [14] previously. The derived values of the ratios C_{PAH}/TM_{PAH} and C_{IN}/TM_{PAH}, 9.0 and 1.7, respectively, agree well with the values reported by Chasis [18] of 7.74 ± 1.86 and 1.41 ± 0.27. (R.P.F. = renal plasma flow; G.F.R. = glomerular filtration rate; TM_{PAH} = maximal tubular excretion of PAH; C_{PAH} = clearance of PAH; C_{IN} = inulin clearance.)

given another course of penicillin, 600,000 units in beeswax and oil daily for 14 days, a total of 8.4 million units. This course of therapy was completed October 15, 1948. The maximal Kahn titer during the relapse was 60 units. This was observed on the day the second course of treatment was begun. Three and one-half months after the completion of the second course of therapy, the Wassermann reaction again became negative. At four months the Kahn titer was only 3 units, and there was no evidence of any relapse lesions and the patient denied the same.

A lumbar puncture during the relapse period revealed a negative spinal fluid Wassermann.

Renal Clearance Studies: Renal clearance studies were made prior to and following the first course of penicillin therapy on the dates indicated (see table). The effective renal blood flow was measured by the clearance of p-aminohippurate * in low plasma concentration (C_{PAH}), and the maximal tubular excretion of this substance was measured by its clearance at high plasma concentration (TM_{PAH}). The rate of glomerular filtration was calculated from the inulin clearance (C_{IN}). The physiologic basis of these measurements has been evolved by Smith.[13] The methods and technics used were those described by Goldring and Chasis.[14] At least three clearance periods were measured at each observation. Since infusion was performed with a constant speed, motor-driven infusion pump, it was possible to calculate clearance according to the simplified method of Earle and Berliner,[15] and to compare results obtained by this method with those of the standard or urine collection technic. There was reasonably good agreement between the two technics. Since the simplified method is not applicable in the presence of edema, it was not employed in the first observation. The last observation employed the simplified method only. In the last study, total PAH after hydrolysis was determined. In the previous studies the method of Bratton and Marshall [16] only was used. From the values for C_{PAH}, C_{IN} and TM_{PAH}, the values for $C_{PAH/TM}$ and $C_{IN/TM}$ were derived. The expression $C_{PAH/TM}$ relates renal plasma flow to the maximal tubular excretory capacity, and indicates the virtual

* Grateful acknowledgment is made of p-aminohippurate supplied by Sharpe and Dohme, Philadelphia, Pa.

quantity of plasma cleared per unit of functional tubular tissue. Values above or below normal indicate a relative hyperemia or ischemia, respectively. C_{IN}/TM_{PAH} is an expression of the rate of glomerular filtration per unit of functional tubular tissue. Variations from the normal indicate imbalance between glomerular and tubular function. The ratio of glomerular filtration to effective renal plasma flow, C_{IN}/C_{PAH}, represents the filtration fraction and is expressed as a percentage. The data derived from these clearance studies are shown in the table.

Discussion

The pretreatment values suggest those seen in acute glomerulonephritis,[17] when the renal plasma flow may be either increased, normal or decreased, the maximal tubular excretory capacity is decreased, and glomerular filtration is depressed, with an invariable reduction in the filtration fraction.

The normal values for the ratios C_{PAH}/TM_{PAH} and C_{IN}/TM_{PAH} indicate concomitant and functionally equivalent depression in renal plasma flow and glomerular and tubular function. The former value is usually elevated and the latter depressed in acute and chronic glomerulonephritis.[17]

After the patient had received penicillin, with prompt clinical improvement, clearance tests indicated healing of the renal lesion and a return toward normal function. Glomerular filtration increased relatively more than did effective renal plasma flow, resulting in a relatively high filtration fraction. This may indicate efferent arteriolar constriction. The patient has been carefully followed for more than one year and at no time has the blood pressure been elevated.

These tests indicate, then, that in the case of syphilitic nephrosis herein presented there was functional involvement of both glomeruli and tubules. This suggests the findings in acute glomerulonephritis, with the exception that neither glomeruli nor tubules were predominantly involved. The term glomerulonephrosis would therefore seem more appropriate. The reduced filtration rate, and consequent impairment of sodium excretion, undoubtedly was a factor in the etiology of the edema which this patient exhibited. Following the administration of penicillin, diuresis occurred at a time when the serum albumin level was low.

This represents the first reported application, to our knowledge, of this form of clearance test in a case of so-called syphilitic nephrosis. Urea clearance and other routine renal functional tests in previously reported cases have shown little or no functional impairment. The value of the type of clearance test employed here in the accurate evaluation of many forms of renal disease is well recognized and warrants emphasis and more widespread application.

Summary

1. A case is reported of so-called syphilitic nephrosis in an 18 year old colored male who was treated with penicillin and studied by means of p-aminohippurate and inulin clearance tests before and after treatment.

2. Tests indicated that there was concomitant and approximately equivalent depression of glomerular and tubular function, suggesting that seen in acute glomerulonephritis. Recovery appeared to be complete.

3. This is the first case of syphilitic nephrosis, to the authors' knowledge, in which PAH and inulin clearance tests have been reported.

ACKNOWLEDGMENT

The authors wish to express their thanks to Dr. Homer W. Smith and Dr. David P. Earle, Jr. for their kind advice in the preparation of this manuscript.

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RHEUMATOID ARTHRITIS WITH DEATH FROM MEDULLARY COMPRESSION *

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Death as a direct complication of rheumatoid arthritis is a distinctly uncommon occurrence, despite the frequency and generalized nature of the disease. Over a 25 year period at the Mayo Clinic, 30 necropsies were performed on cases of rheumatoid arthritis and among these there were no neurologic deaths.[1] We have recently had the opportunity of observing a case in which demise was felt to have resulted from compression of the medulla oblongata by the odontoid process. The herniation of this process was secondary to destructive osseous changes of rheumatoid arthritis.

Case Report

A 58 year old physician's wife was admitted to The Johns Hopkins Hospital, on the service of Dr. Charles Wainwright, February 21, 1948, complaining of "difficulty in breathing." The father of the patient had had rheumatic fever and one sibling had had a cerebral vascular accident, but the family history otherwise was noncontributory. For many years the patient had noted the presence of multiple firm nodules about her scalp. She had undergone a hysterectomy in 1944, presumably for fibromyomas. For an indeterminate period of time she had received Ertron intermittently, but none during the one year prior to admission.

The present illness began 25 years prior to admission, at which time the classical symptoms of rheumatoid arthritis were first manifested, initially involving the knees, later spreading to encompass all of the small and weight-bearing joints. Over this long period, gradually progressive flexion contractures and limitation of motion occurred. Six years before admission she reached a stage of disability prohibiting further ambulation and became a chair-ridden invalid. Nine years before admission she fractured her right hip, and a pin was inserted; five years later this was removed because of penetration through the acetabulum. Three months prior to admission she developed an upper respiratory infection, during which she noted the onset of bilateral auditory impairment, which progressed rapidly to almost total deafness. At approximately the same time there developed dysphagia and laryngeal stridor, both of which persisted until admission. One month later her voice became coarse and rasping. On the day of admission she became dyspneic, with a sense of obstruction "in my throat."

Physical examination on admission revealed normal temperature, pulse and blood pressure. The respiratory rate was 22, and loud expiratory laryngeal stridor was evident. She was a well developed and well nourished middle aged woman who appeared chronically ill and in acute respiratory distress. The skin was pale, atrophic and somewhat inelastic. Scattered over the cranium were multiple irregular firm nodular areas, presumed to be attached to bone. Over the occiput and about the left pinna were chronic ulcerations with small amounts of purulent discharge. The eyes were not remarkable except for minimal retinal arteriosclerosis. There was moderately advanced, bilateral conduction-type deafness. The tongue revealed several small ulcers, felt to be secondary to trauma. Mirror laryngoscopy demonstrated limitation of abduction of both vocal cords, though each moved somewhat; a small

* Received for publication June 7, 1949.
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amount of mucus was retained in the pyriform sinuses. The neck was unduly short, but moderate range of motion was present. The chest was asymmetrical, the right appearing fuller, with fair excursion bilaterally. The lung fields were hyperresonant, the breath sounds of good quality, though obscured by the stridor. There were scattered moist râles at both bases and in the left axilla. The heart was grossly normal, as was the abdomen. Pitting edema was present in both lower extremities, more marked on the right. The entire skeleton was involved by advanced rheumatoid arthritic changes, with multiple flexion contractures and subluxations; there was marked impairment of motility throughout, especially in the legs, where almost complete ankylosis had occurred in all joints. No abnormalities could be demonstrated in the neurologic examination, exclusive of the cranial nerve changes described above. (Adequate neurologic survey was limited by the extensive skeletal changes.)

Laboratory studies were entirely within normal limits, with the exception of the roentgenograms and electrocardiogram. The former revealed extensive destruction of the articular surfaces of the heads of both humeri, with similar changes in the glenoid fossae; there was generalized osteoporosis; the femoral heads showed almost complete destruction, with protrusion of the acetabula into the true pelvis. Unfortunately, adequate roentgen examination of the cervical spine was not obtainable because of marked deformity and pain. There was calcification of the blood vessels of the legs. The electrocardiogram was interpreted as indicating nonlocalizable and nonspecific myocardial involvement (isoelectric or diphasic T waves in the conventional limb leads, and $CF_{1, 2 \text{ and } 6}$).

The hospital course was characterized by progressive deterioration, with gradually increasing laryngeal stridor, dysphagia and dyspnea. During the first six hospital days respiration was adequately maintained, but through the ensuing four days it became more difficult, until terminally only two respiratory cycles each minute were observed for several hours. Demise was precipitated by vomiting and accumulation of mucus in the tracheobronchial tree on the tenth hospital day. The clinical impression was acute bulbar failure of undetermined etiology, and severe rheumatoid arthritis.

The pertinent necropsy findings, as well as the complete anatomic diagnosis, are briefly summarized below.

On examination of the base of the skull from above there was an obvious mass, about 1 cm. in diameter, raised 0.5 cm. above the surface of the occipital bone just in front of the foramen magnum. This mass clearly impinged on the inferior surface of the medulla, forming a definite depression there and compressing this structure significantly at a point just below the pons. Sagittal section of this bony region showed the mass to be odontoid process which had herniated upward through the foramen magnum. The anterior arch of the atlas and possibly a portion of the occipital bone immediately surrounding this process were soft, appearing to be replaced by both fibrous and necrotic tissue. The overlying dura was smooth.

Microscopic sections of the region of the herniated odontoid process showed evidence of bone destruction and fragmentation, as well as fibrosis and new bone formation. Several areas of fresh collagen necrosis typical of active rheumatoid disease were seen both here and in sections of other joints.

The ganglion cells of the medulla showed pyknosis, eccentric nuclei and vacuolization of cytoplasm. No demyelinization was evident, and sections of other areas of the brain and cord were normal.

Anatomical diagnosis: Rheumatoid arthritis with widespread deformity and ankylosis of joints; skeletal muscular atrophy with associated round cell foci; focal collagen degeneration in myocardium and about joints; periarterial fibrosis in spleen; generalized osteoporosis; herniation of cervical spine into foramen magnum, with pressure of odontoid process on medulla; perforated esophageal ulcer with subacute

osteochondritis of cricoid cartilage and bilateral fistulous tracts beneath laryngeal mucosa; left lower lobe atelectasis; calcific deposits in renal tubules (history of vitamin D therapy); focal cortical scarring of kidneys; chronic cystitis; fatty infiltration of liver (periportal); atrophy of pancreas; thyroid adenomas; generalized arteriosclerosis; surgical absence of uterus, tubes and ovaries; encapsulated tuberculosis primary complex of left lung.

Discussion

Compression of the medulla or cervical spine following fracture, displacement or compression of the upper cervical spine has been occasionally observed. A discussion of the mechanics of this vital area is beyond the scope of this paper, and for details the reader is referred to the reports of Bézi [2] and Berkheiser and Seidler.[3]

Congenital disorders of the atlanto-axial-occipital joint may lead to cord or medullary compression. This group includes congenital basilar impression, Arnold-Chiari and Klippel-Feil syndromes, spina bifida and assimilation.[2, 4, 6] Likewise, trauma may result in fatal structural alterations of these joints; forced bending of the cervical spine may fracture the axis or atlas, although this occurrence is rare.[7] Odontoid fracture, when displacement of this process occurs, is a well known cause of fatal medullary compression.

Dislocation of the occipito-atlanto-axial joint may arise in association with any inflammatory process in the neck, presumably due to capsular and ligamentous distention, hyperemia and muscle spasm; diseases in which this complication has been observed are mastoiditis, rheumatic fever, periostitis, following tonsillectomy and/or adenoidectomy, nasopharyngitis, lymphadenitis, and retropharyngeal abscess.[3, 8, 9, 10]

In addition to congenital lesions, trauma and acute contiguous infections, there is a heterogeneous group of diseases which have produced sufficient bony destruction of the atlas, axis and occiput to result in medullary compression. Included in this category are tuberculosis, syphilis, osteomyelitis, neoplasm, actinomycosis, echinococcosis, hemangioma, Paget's disease, hyperparathyroidism and rickets.[2, 4, 8, 11, 12] In addition to luxation, compression and fracture, several of this group may lead to the associated development of meningitis.

Rheumatoid arthritis, or Marie-Strümpell spondylitis, commonly involve the spine, and the upper cervical vertebrae are occasionally affected. Compression of the spinal cord by the extreme flexion sometimes observed in these processes has been recorded.[13] Dislocation of the atlanto-axial joint has been observed in active rheumatoid arthritis, with manifestations of medullary compression.[8, 14] A review of the English literature, however, has failed to reveal a fatal case of medullary compression on this basis in which other diseases of the occipito-atlanto-axial joint were absent, and a review of the necropsies at The Johns Hopkins Hospital has likewise yielded no similar case.

In the present instance, it seems probable that the rheumatoid arthritic process, which had been active for many years, gradually produced bony destruction of the axis, atlas and occiput similar to that which occurred in the other weight-bearing joints. As necrosis and fragmentation advanced, compression and resulting deformity ensued. Herniation of the odontoid process was eventually of sufficient magnitude to encroach on the vital centers of the medulla, especially the respiratory center, and death resulted.

SUMMARY

A case is reported of chronic severe rheumatoid arthritis, with destruction and osteoporosis of the occipito-atlanto-axial joint of sufficient magnitude to allow herniation of the odontoid process through the foramen magnum, resulting in fatal medullary compression. This is presumably the first such case recorded in the English literature.

ACKNOWLEDGMENT

Acknowledgment is expressed to Dr. Morgan Berthrong for reviewing and summarizing the necropsy findings.

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PRIMARY THROMBOSIS OF THE AXILLARY AND SUBCLAVIAN VEINS *

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PRIMARY thrombosis of the axillary and subclavian veins can be defined as a thrombosis of these veins occurring after some unusual violent muscular effort or, as is more frequent, following a trivial muscular strain or indirect trauma. Such

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rare cases as occur after no apparent muscular effort should be considered as primary, although a careful history will often reveal some unusual mechanical factor accounting for the condition. There is no doubt, however, that a very small group of cases do occur with no obvious etiology. This condition has been referred to as "thrombosis by strain," "spontaneous thrombosis," "idiopathic thrombosis" or "traumatic or effort thrombosis." Primary thrombosis should be distinctly separated from axillary thrombosis as a result of direct injury, from thrombosis occurring during the course of a systemic disease such as polycythemia or heart failure, from thrombosis with postoperative scarring or adjacent infected tissue, or from thrombosis associated with invasion or compression of the vein by neoplastic tissue.

Primary thrombosis of the axillary and subclavian vein is a relatively rare condition, as evidenced by the fact that most reports on the subject deal with but one or two isolated instances. The condition was described in 1875 by Paget [1] as "gouty phlebitis," and cases reported by Mackenzie in 1862 and by Humphrey in 1869 were mentioned, but the first adequate clinical record was by Von Schroetter [2] in 1884. From that time until the classical account of the condition by Dr. Rudolph Matas [3] in 1934, approximately 100 cases were reported. In 1942 DeBakey, Ochsner, and Smith [4] collected an additional 50 cases. Sporadic reports [5, 6, 7, 8, 9, 10, 11] have continued to appear, but the eight cases presented by Gould and Patey [12] in 1928 still constitute the largest single series. More recently Kaplan [13] reported a series of five cases, and Sampson,[14] in his excellent review of the subject, likewise presented five cases. Veal and Hussey [15] in 1943 presented 46 instances of thrombosis, but only six of these can be classified as primary. The following case is presented to emphasize again the trivial nature of the responsible trauma.

Case History

The patient, a well developed and well nourished 23 year old white male, had always considered himself in excellent health. He had been employed for several years in the performance of light labor consisting of moving small packages from one cart to another. He did very little if any overhead or heavy lifting, and in the days immediately preceding his illness had performed no strenuous physical labor, nor was he aware of any body trauma.

Three days before admission to the hospital, on May 18, 1948, while at work, the patient became conscious of a tightness of the sleeve of his right arm. There was no pain, local heat or generalized symptom. He continued to work, aware, however, of an increasing swelling in his right arm. On the following day the patient noticed that his arm was still enlarged, with some warmth but no redness. He consulted a physician and was given oral penicillin, but on the third day, because of the persistent swelling, was admitted to the hospital.

On physical examination, the entire right arm, hand and tissues about the shoulder and pectoral region were swollen. The skin had a light purplish discoloration, and the superficial veins were prominent and failed to collapse on elevation. One small, well-healed scratch on the dorsal surface of the third right finger was present, but there was no evidence of infection. The patient was of athletic build, with well-developed muscles about the neck and shoulders. The temperature and pulse were normal, as was the remainder of the physical examination.

The white blood cell count was 6,400 with a normal differential, and the remainder

of the routine laboratory procedures were normal. The venous pressure in the right antecubital vein was 300 mm. of water; in the left it was at a normal level of 110 mm.

A diagnosis of spontaneous or idiopathic thrombosis of the subclavian vein was made. The arm was elevated and covered with warm dressings, and anticoagulant therapy with heparin and Dicumarol was initiated. During the next few days these local measures were continued, and the prothrombin concentration was maintained below 30 per cent with the use of Dicumarol. Eight days after admission the venous pressure in the right arm had fallen to 240 mm. of water, as compared with the original pressure of 300 mm. of water. Although there was slight swelling of the arm, the patient was practically symptom-free and was dimissed from the hospital.

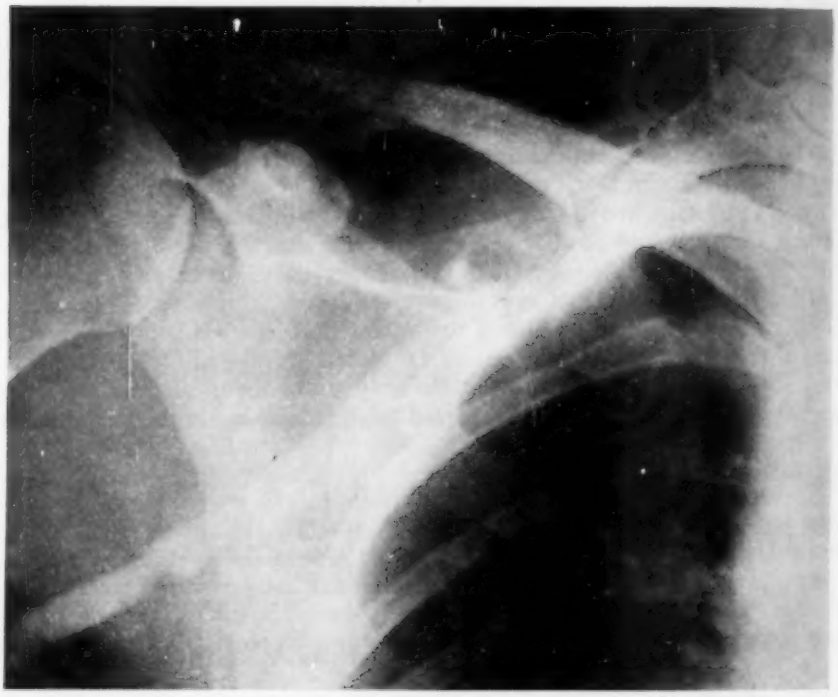

FIG. 1. Diodrast injection into the right antecubital vein (June, 1948), showing distention of the axillary and subclavian veins. The diodrast visualization disappears at the outer border of the first rib. Considerable collateral circulation is visualized above the right clavicle.

One month after the onset of the thrombosis the venous pressure was 225 mm. of water. A roentgenogram of the right arm and shoulder following diodrast injection into the right antecubital vein showed the axillary and subclavian veins to be enlarged and distended. No diodrast was visualized beyond the subclavian vein in the region of the first rib, but numerous small collateral vessels were clearly seen in the area (figure 1). Because of the persistent edema, a cervicothoracic sympathetic block was performed which resulted in temporary warmth of the right arm and diminished swelling. The patient was permitted gradually increasing exercise, with care to avoid elevation or strain of the right arm. On September 18, 1948, four months following the thrombosis, there was still some mild edema of the arm and the venous pressure

was 160 mm. of water. The patient had little or no discomfort with his arm and was permitted to return to work.

On November 24, 1948, six months after the thrombosis, the venous pressure was 135 mm. in the right arm and 120 mm. in the left. There was still very mild edema of the arm, but the patient had been at work for two months with almost no complaints. A roentgenogram of the right arm and shoulder following diodrast injection was repeated in November, 1948 (figure 2). This clearly demonstrated the axillary and subclavian veins, but these were not distended as demonstrated in the initial roentgenogram, and the collateral circulation about the subclavian vein was not evident.

FIG. 2. Diodrast injection into the right antecubital vein (November, 1948), showing a reduction in the distention of the axillary and subclavian veins and an absence of evident collateral circulation.

On this visit, with the venous pressure apparatus in the involved extremity showing 135 mm. of water, pressure was placed on the anterior pectoral muscles just below the right clavicle. Immediately the pressure in the manometer rose to over 200 mm. of water, demonstrating the function of the collateral circulation (figure 3). Pressure in a similar area on the uninvolved side resulted in no rise in the venous pressure in the left arm.

The patient was last seen in June, 1949, 13 months after the onset of the thrombosis. He had been at work steadily and complained only of some apprehension over the prominence of the veins of the right arm, especially after exercise. There was no pain, and no discomfort. On examination, the veins of the right arm were more distended than those of the left, and the venous pressure in the right antecubital vein

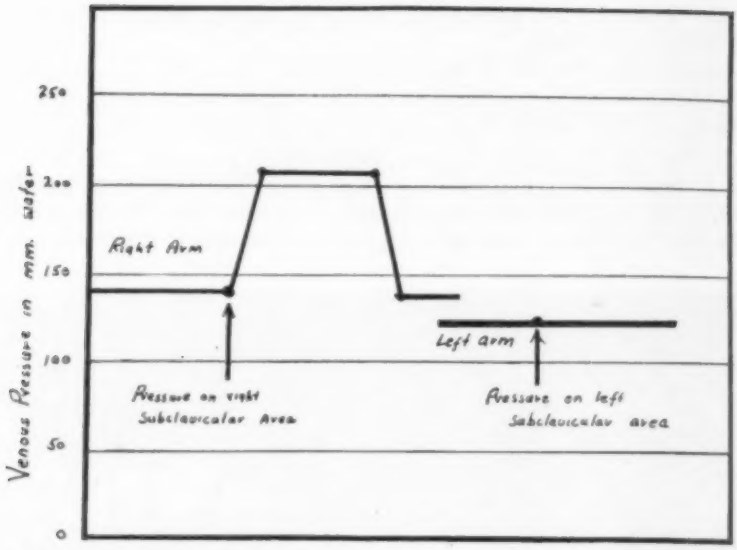

FIG. 3. Graph demonstrating the slight elevation of venous pressure (140 mm.) in the right arm six months after the thrombosis as compared with the normal pressure in the left arm (120 mm.). With pressure on the right subclavicular area, the venous pressure rose immediately to 210 mm. A similar rise was not obtained when pressure was exerted over the left subclavicular area.

was 140 mm. of water as compared with 120 mm. of water on the left. Exercising the hand and pressure over the subclavicular area did not result in a rise of the venous pressure. The progressive fall in the venous pressure throughout the course of the patient's illness can be followed in figure 4. The patient was reassured and he returned to full work.

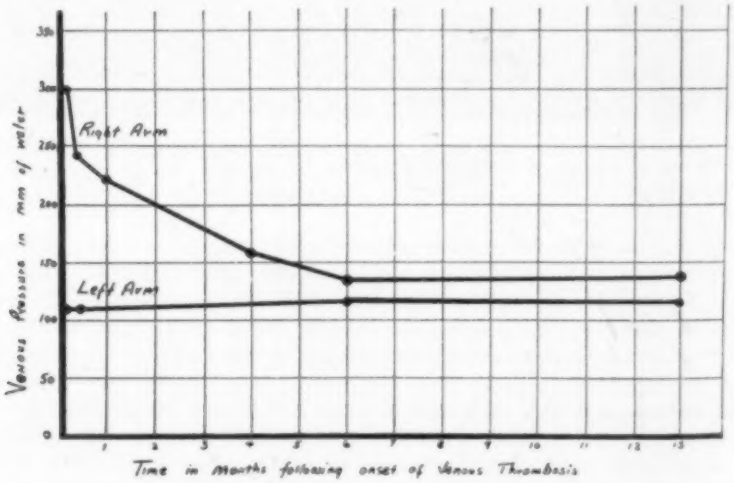

FIG. 4. Graph demonstrating the progressive fall toward normal of the venous pressure in the right arm as compared with the normal venous pressure in the left arm.

Discussion

Many explanations have been offered for this unusual condition, but most of the studies have pointed to a traumatic basis and have been directed toward anatomic investigation. Most workers have stressed the mild nature of the trauma, and typical cases have been reported following such insignificant acts as throwing a ball, lifting a heavy weight, winding a jack, or even reaching overhead. In 1884, in the original description of primary axillary venous thrombosis, Von Schroetter [2] felt that the thrombosis resulted from a sudden stretching and compression of the vein, but he offered no explanation as to the mechanism of the involved forces.

Early workers presented several hypotheses, which involved various compression forces against the subclavian and axillary veins associated with insignificant trauma or strain as being responsible for the thrombosis. Different investigators presented these various forces as being the medial border of the pectoralis minor muscle,[16] the subclavius muscle,[12] the clavicle or the first rib.[17] As early as 1910 it was felt that increased respiratory effort had some compressing effect on the subclavian vein and contributed to the thrombosis.[18, 19] Lowenstein [20] in 1924, from exacting anatomic dissections, showed that a compression of the axillary vein was caused by the costocoracoid ligament as it crossed the vein at a point just distal to the crossing by the vein of the first rib, and for many years this was the commonly accepted theory.

In 1935, Veal and McFetridge [21] postulated the theory that compression of the axillary vein, which was responsible for the thrombosis, occurred between the abducted head of the humerus and the subclavian muscle. They fortified their belief (which was at variance with Lowenstein's theory) by diodrast injection demonstrating the constriction of the axillary vein in the abducted position.

Sampson, Saunders, and Capp [22] in 1940 presented the hypothesis that, in certain types of individuals with high, horizontally curving first ribs and upward and backward directed clavicles, there is a partial compression of the subclavian vein in the first third of its course. In these individuals a backward thrust of the shoulder girdle, without necessarily abducting or elevating the arm, will increase the degree of subclavian compression and, in some cases, result in thrombosis. Sampson [14] later presented cases of primary axillary thrombosis of the vein that illustrated the significance of this anatomic factor.

In all of these anatomic explanations of primary thrombosis of the axillary or subclavian vein, there is the introduction of some strain or trauma, no matter how trivial, to account for the condition. Probably no one theory can account for all of the cases, and it seems likely that thrombosis may take place at different points in the axillary and subclavian veins, depending on the type of strain or muscular movement or on the individual anatomic variation.

Primary among other hypotheses offered for this condition is the one of sympathetic venous spasm. Cottalorda [23] in 1924 first suggested that venous spasm was initiated by trauma, with resulting thrombosis and edema. However, the development of a thrombus in the vein does not necessarily always follow, and cases have been reported in which, at operation, the axillary vein was found in a state of marked spasm but with no thrombosis.[23, 24, 25] Cottalorda also called attention to the fact that mere obstruction of the vein itself is not necessarily a prerequisite to the developing edema, but that the irritation of an inflamed or injured

perivenous plexus in the venous wall can be responsible for the rapid and persistent swelling. More recently, similar views have been expressed by Ochsner and DeBakey [26] as to the origin of edema in thrombophlebitis. However large a part venospasm may play in the production of the symptomatology of this condition, certainly it is not the primary cause of the thrombosis.

Other factors, such as chemical changes in the blood or a slowing of the venous flow, have been considered in the etiology.[6, 7, 20] These factors are important in thrombosis secondary to other conditions, but they are not responsible for primary axillary or subclavian venous thrombosis. Thorough investigation has eliminated infection as a cause.[3] Finally, there remain a few instances that defy any explanation, and it has been the opinion of some workers [27] that too little attention has been paid to the apparently spontaneous nature of these cases and too much importance attached to an insignificant traumatic episode in an attempt to explain the mechanism.

To summarize the etiology, it seems that the exact cause of this condition is still in doubt. Trauma, however mild, constitutes the basic factor, and the condition appears especially in certain individuals with a predisposing anatomic configuration, at times aided by the factors of circulatory slowing and respiratory movements. Very likely, in some patients certain factors are more pronounced than in others, where they may even be absent. In spite of all studies, there remains a small group of cases in which the etiology is still obscure.

The symptoms of primary axillary and subclavian venous thrombosis are primarily those of sudden venous obstruction and associated vasospasm with an absence of the local or constitutional sign of inflammation. The onset is acute and usually, but not always, follows some trivial indirect traumatic incident or the performance of some repetitious action involving the use of the shoulder. The condition occurs two and one-half times more frequently in the right arm than in the left,[28] and characteristically it is found in an active male between the ages of 20 to 40 with well developed neck and shoulder muscles. There is an initial sense of fullness of the involved extremity and a dull generalized aching, but only rarely is severe pain present. Within several hours the entire extremity, as well as the anterior chest wall, is enormously swollen. There is an associated arterial spasm, so that often the arm is cool and slightly cyanotic, with definite blueness of the fingertips. The arterial saturation on the affected side is considerably reduced.[9, 10] The superficial veins are prominent, and in some cases a tender cord can be felt in the axilla. Blood pressure readings in the two arms are usually equal,[2, 6, 10, 13, 14, 27] although the venous pressure in the involved extremity is greatly elevated and the circulation time prolonged. There is rarely an elevation of the leukocytes, and the erythrocytes remain the same on the two sides. Other hematologic studies—the bleeding time, the platelet count and the clotting time—remain normal.[2, 9, 10] The temperature and pulse are unaffected. The arm is usually rendered quite useless in the initial stages, and the patient commonly supports it with the uninvolved extremity.

In initiating treatment, the patient should be placed at bed-rest with the arm elevated, immobilized and encased in warm, moist dressings. Such procedures will tend to reduce the venous and arterial spasm and promote a more rapid subsidence of the edema. Movements of the hand should be encouraged. In view of the thrombotic nature of the lesion, anticoagulants are indicated. Pulmonary embolism has been reported on but two occasions,[29, 30] but heparin and Dicumarol

will reduce the local propagation of the thrombus into the surrounding tributaries, and thus reduce the degree of obstruction and resulting edema and aid in the establishment of collateral circulation. Hughes [31] has recently reported the use of Dicumarol in this condition. As the acute symptoms subside, usually within several days, the patient may be allowed up and about, his arm in a sling and restricted to moderate activity.

Temporary cervicodorsal sympathetic block, as advocated by Ochsner and DeBakey,[26, 32] may be utilized to reduce the vasospasm and edema, and some workers have found benefit from this procedure even a month after the onset of the thrombosis.[33] In the present case, the beneficial results were only mild and were not permanent.

In cases with persistent incapacitating edema or pain, or in those with recurring episodes, a surgical approach is indicated. The exact procedure may vary with the finding, and one may excise a segment of the vein or remove the obstructing thrombus, although the latter procedure has usually been unsatisfactory. By such procedures some workers [34, 35] have produced a prompt subsidence of the edema after a trial of several months of medical therapy.

It is evident that such cases may assume a medico-legal aspect, particularly in those instances where symptoms arise apparently spontaneously in an individual performing some relatively simple action. It might be well to emphasize that a distinct difference should be recognized between those cases occurring from muscular strain or indirect injury, no matter how slight, and the group, likewise termed spontaneous, in which there is an absolute absence of any history of accident, antecedent injury or continued occupational strain. The absence of such accidental trauma, whether direct or indirect, trivial or severe, excludes the nontraumatic cases from the category of accident insurance liability.[3]

One must exercise caution in returning these patients to their jobs. All workers have stressed the high percentage of recurrences when these individuals resume the type of work they were performing when the thrombosis occurred, no matter how trivial the strain might have appeared.

The prognosis for life is excellent, and no death has been reported. As for prolonged disability, however, the prognosis is not so encouraging. The case reported by Matas [3] was disabled after four years, and his disability was substantiated by court action. An excellent guide to the progress of the condition is the level of the venous pressure in the involved extremity. Veal and Hussey [15] demonstrated that, even in the absence of edema, some cases may have a normal venous pressure at rest but may develop a decidedly abnormal rise if the involved arm is exercised. The present case demonstrated the abnormal rise in venous pressure with pressure over the area of the collateral circulation (figure 3). A common complaint in these individuals is a persistent sense of heaviness or dull aching whenever the arm is exercised. The usual case, however, is relatively free of symptoms and able to resume light work within several months, although slight enlargement of the arm may persist for a longer time.

Conclusion

A case of spontaneous thrombosis of the subclavian vein has been presented, with a review of the etiology, symptomatology, treatment and prognosis of this condition.

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MYASTHENIA GRAVIS: REPORT OF CASE RECEIVING UNUSUAL DOSAGE OF NEOSTIGMINE *

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Introduction

Myasthenia gravis, an endocrine or metabolic disease characterized by excessive fatigability of skeletal muscle, eluded all attempts at treatment until Edgeworth [1] in 1930 found that ephedrine was beneficial. Then Walker [2] in 1935 introduced neostigmine, which has remained the best and most commonly used therapeutic agent to date. Recently cholinesterase inhibitors have been used with varying promise. Among these have been "DFP," diisopropyl fluorophosphate used by Comroe,[3] "HETP," hexaethyltetraphosphate, employed by Westerberg,[4] and "TEPP," tetraethylpyrophosphate, first tried clinically by Burgen.[5] Surgical approach began in 1913, when Sauerbruch [6] employed thymectomy, but it remained for Blalock [7] in 1939 to perform the first successful total thymectomy for a tumor associated with myasthenia gravis. Subsequently, thymectomy series have been reported by Blalock,[8] Keynes,[9] Clagett,[10] Viets,[11] Adams [12] and others.

Thymectomy was performed in one of our recent cases who was refractory to medical management, even though the dosage of oral neostigmine administered (1,260 mg. per 24 hours) was larger than any found previously recorded. After operation, 336 mg. of neostigmine parenterally was required in a 24 hour period. These unusually large dosages of neostigmine, in addition to the use of one of the newer cholinesterase inhibiting drugs and certain other aspects of the postoperative course, make it seem desirable to report this case in detail.

* Received for publication June 28, 1949.
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Case Report

An 18 year old married colored woman entered the John Sealy Hospital in March, 1948, complaining of generalized weakness of three months' duration. Onset occurred January, 1948, with drooping of the right eyelid followed by drooping of the left and weakness of the legs and arms. In four weeks' time the left eye shut almost completely, the patient could neither walk nor get out of bed, and there was difficulty in chewing and swallowing. Her local physician, recognizing myasthenia gravis, prescribed one ampule (1 c.c. of 1:2000) neostigmine methylsulfate one-half hour before meals. Since on this régime the patient was barely able to get out of bed to eat, she was admitted to this institution for further treatment.

On admission the past history and review of systems were not significant. There were two children, the last born in September, 1947. The physical examination revealed normal blood pressure, temperature, respiration and pulse. The heart, lungs and abdomen were normal to physical examination, and the extremities showed no atrophy or deformity. Sensation was normal and no abnormal reflex was present. There were, however, ptosis of both eyelids, weakness of all extremities, disappearance of active reflexes on repetition, and inability of the patient to sit up or chew. Laboratory studies revealed normal blood, urine, serologic test for syphilis, blood chemistry, electrocardiogram and muscle biopsy. Roentgenogram did not show mediastinal tumor.

Since initially 30 mg. of oral neostigmine bromide 30 minutes ante cibum were barely sufficient for chewing and swallowing, the dose was increased until, on the thirty-sixth hospital day, 1,260 mg. per 24 hours were begun. Usually the 2 a. m. and 4 a. m. doses were omitted. Together with atropine sulfate, 0.65 mg. five times daily, and ephedrine sulfate, 0.25 gm. four times daily, this régime enabled the patient to get up and walk around the bed by holding on. This heavy dosage of neostigmine, however, while giving no evidence of toxicity, caused but little more improvement than somewhat smaller doses. Intramuscular administration of neostigmine revealed that 2 mg. (four ampules of 1:2000) of drug corresponded in effect to 105 mg. orally, roughly conforming to the 1:30 ratio of effectiveness of the oral and intramuscular routes.

A simple hyperplastic thymus, weighing 32.8 gm., was removed on the forty-third hospital day through a trans-sternal approach. Neostigmine, 1.5 mg. every hour intramuscularly, was given throughout the operation and continued postoperatively. Immediate recovery in an oxygen tent was quite satisfactory. At 5 p. m. oral neostigmine, 105 mg. every two hours was begun to supplement the intramuscular injections, but, because of a misunderstanding, the intramuscular administration was stopped at this time. The patient did well until 6:30 a.m. of the next day, when she suddenly developed dyspnea, weakness and much mucus and saliva which she could not expectorate or swallow—a typical myasthenic crisis. Gastric dilatation, accounting for the failure to absorb neostigmine, was noted, and Wangensteen suction was begun. She was placed in a Drinker respirator and the pharynx was aspirated frequently. Neostigmine intramuscularly 1.5 mg. every 30 minutes, was given with atropine, 0.43 mg. every two hours, ephedrine sulfate, 0.25 gm. every four hours, and potassium chloride, 3.0 gm. intravenously. Since there was an increase in strength shortly after each neostigmine injection, the dose was increased to 1.5 mg. every 15 minutes, with further improvement. An intratracheal tube was necessary for an unobstructed airway, and intranasal administration of oxygen was started. When the patient became weaker, the neostigmine was increased to 2.5 mg. (five ampules) every 15 minutes, with improvement to the point of her being able to write notes to the attendants, such as "I want a pillow," and "Turn me on my side," but she was unable to breathe without a respirator.

When she appeared weaker the second postoperative day, neostigmine was increased to 3.5 mg. (seven ampules) every 15 minutes, with improvement. Atropine and ephedrine were continued in the same doses through the fourteenth postoperative day. Penicillin was begun. Nutrition was maintained by intravenous fluids, vitamins and protein hydrolysates. Frequent pharyngeal aspirations removed much mucus and saliva, but the tendency of secretions to gravitate into the trachea necessitated reinsertion of the endotracheal tube after laryngoscopy. The glottis and cords were slightly reddened but not edematous. Respiratory exchange was good in the respirator but almost nil without it.

Late in the third postoperative day the patient appeared weaker. There were muscular twitchings and moderately dilated pupils which did not react to light. The conjunctivae were edematous, and there was bilateral bronchopneumonia with a tem-

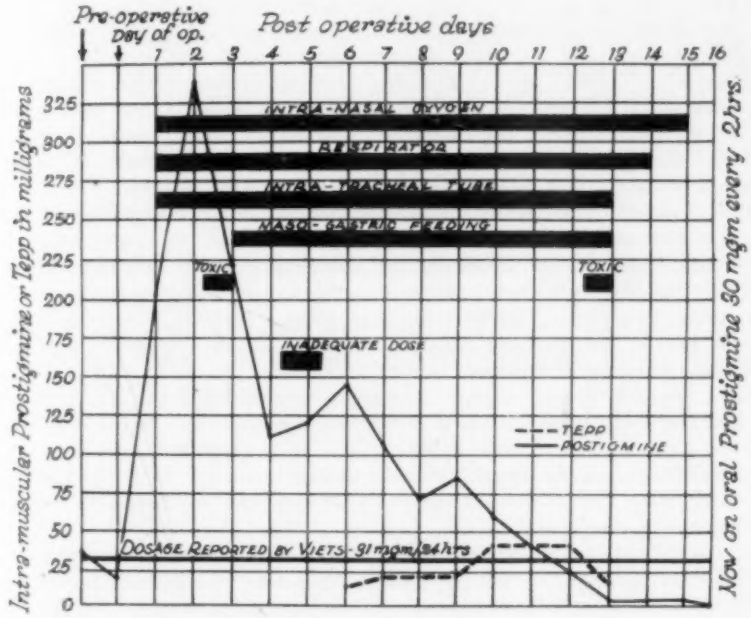
Pre-operative
Day of op.
Post operative days
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Intra-muscular Prostigmine or Tepp in milligrams
325 300 275 250 225 200 175 150 125 100 75 50 25 0
Now on oral Prostigmine 30 mgm every 2hrs.
INTRA-NASAL OXYGEN
RESPIRATOR
INTRA-TRACHEAL TUBE
NASO-GASTRIC FEEDING
TOXIC
TOXIC
INADEQUATE DOSE
TEPP
POSTIGMINE
DOSAGE REPORTED BY VIETS-91 mgm/24 hrs

FIG. 1. Graph showing neostigmine (prostigmine) and TEPP dosage in milligrams intramuscularly every 24 hours. Other drugs used were: Atropine .43 to .65 mg. 2 hrs. (hypo); ephedrine 25 mg. 4 × 1 day (hypo).

perature of 103.6 (R). Since she was receiving 672 ampules (336 mg.) of neostigmine per 24 hours, the problem was whether the increased weakness was due to neostigmine intoxication or whether, with the pneumonia and fever, an insufficient amount was being given. The former seemed more likely, so the dosage was gradually reduced to 1.5 mg. (three ampules) every 15 minutes, resulting in improvement in strength. The pupils began to react to light but became almost pinpoint.

On the fourth postoperative day she was able to breathe for 15 to 20 minutes every two to three hours outside the respirator, so that neostigmine was further reduced to 1.5 mg. every 35 minutes, but returned to 1.5 mg. every 15 minutes when weakness recurred. The pupils had become normal in size and reacted to light, indicating that the dosage was not toxic. A paravertebral block was done for thrombophlebitis resulting from ankle cutdown. The endotracheal tube was replaced after cleaning. The

false cords appeared red and slightly swollen. The true cords were in abduction but were covered with a thin grayish-white exudate.

From the fifth to the twelfth postoperative day the patient gradually improved but required constant observation and adjustment of the dosage of neostigmine down to 0.5 mg. every hour. On the arrival of "TEPP" on the sixth postoperative day, this was begun at the rate of 2.5 mg. intramuscularly, and increased to 10 mg. four times daily by the tenth postoperative day. It was continued at this rate until the thirteenth postoperative day. Oxygen intranasally was continued, and the intratracheal tube was cleaned daily before reinsertion, although the patient could breathe for several hours prior to developing a laryngeal stridor which did not respond to topical adrenalin. Intravenous fluids were supplanted by a feeding administered through an indwelling nasogastric tube. The temperature slowly fell as the pneumonia resolved, and she began gradually to spend up to 10 to 20 minutes each hour outside the respirator.

On the thirteenth postoperative day she became toxic again, with moderately dilated pupils which did not react to light, weaker grip, and excessive perspiration and salivation. "TEPP" was discontinued and neostigmine was omitted for three hours, after which 0.5 mg. was given intramuscularly at 90 minute intervals for four doses and then discontinued for 10 hours. The pupils became pinpoint, then dilated, but reacted to light as the toxic symptoms gradually disappeared. Muscle strength returned, and there was a diminution of salivation and perspiration.

On the fourteenth postoperative day the patient, now greatly improved and able to eat, was removed from the respirator, and neostigmine, 0.5 mg. was given every one and a half hours. The following day nasal oxygen and ephedrine were discontinued. By the sixteenth postoperative day, 30 mg. neostigmine orally replaced the intramuscular injections. Temperature was normal and the chest was clear. The voice was hoarse, but distinct; vocal cords were slightly edematous but showed no ulcerations. The patient had now become ambulant.

During the next several days, as her voice improved and the cords healed it was found that she did best on 30 mg. of neostigmine orally every two hours, with omission of the 2 a.m. and 4 a.m. doses. Now able to walk about the ward and care for her personal needs, she was no longer a nursing liability. Later, "TEPP" 5 mg. was given orally twice daily, and its combination with neostigmine was found to be more effective than neostigmine alone.

She was thus discharged at the end of June, 1948, on 300 mg. neostigmine per day along with 10 mg. "TEPP" per day orally. She was re-admitted to the hospital in October, 1948, with little further change in her general condition. On this admission it was found that by discontinuing neostigmine she could tolerate 16.8 mg. of "TEPP" per day orally. However, she still had some generalized weakness. At higher dosage levels she had toxic symptoms as before, namely, miosis, perspiration, salivation, nausea and vomiting. Finally it was found that the addition of 60 mg. neostigmine bromide per day enabled her to be up and around at will. She was last seen in the out-patient clinic in April, 1949. Still on this régime, she stated that she could do her housework but could walk only short distances. There was no difficulty in eating. She had no ptosis of the eyelids.

Summary and Conclusions

A severe case of myasthenia gravis, receiving 1,260 mg. of neostigmine orally per 24 hours without toxic manifestations but with poor response, was subjected to thymectomy. The patient developed an acute myasthenic crisis 18 hours postoperatively from lack of neostigmine due to gastric dilatation. The stormy, difficult postoperative course that resulted responded to the following intensive

measures: (1) constant 24 hour care and observation by special nurses and the house staff; (2) Drinker respirator for 13 days; (3) intratracheal tube for 12 days; (4) neostigmine intramuscularly, reaching a dosage of 336 mg. per 24 hours, a dosage much greater than any previously recorded in the literature (31 mg. per 24 hour period [13]); (5) atropine sulfate, ephedrine sulfate and "TEPP," an anticholinesterase agent; (6) penicillin, oxygen intranasally, paravertebral block, intravenous nutrient fluids, and nasogastric feedings, and (7) almost constant pharyngeal and tracheal aspirations, as well as bronchoscopy as needed.

"TEPP" appeared to be a valuable supplement to neostigmine in this case. Toxicity does occur however and, as shown here, may last as long as 24 hours. It is suggested that in addition to the usual toxic symptoms, a further valuable sign of toxicity of neostigmine or "TEPP" is the size of the pupil and its ability to react to light. It is believed that one of the first signs of toxicity can be a small pupil, which later becomes pinpoint and finally dilated and fixed as toxicity progresses. As toxicity decreases the pupil returns through the same stages in reverse order. This pupil was not affected by 0.65 mg. of atropine given every two hours.

Attention is also called to the possibility that difficulties in the management of other postoperative cases may be due to failure to recognize neostigmine toxicity, curare-like in over-dosage, or failure to supply the tremendous amount of neostigmine necessary in the face of complications.

It is impossible to evaluate completely the effect of thymectomy in this case, since she has subsequently been maintained on a combination of "TEPP" and neostigmine. After operation she was improved on approximately one-fourth the preoperative dosage of neostigmine, but certainly the effect of thymectomy could hardly be called striking.

Acknowledgment

"TEPP" was quickly and generously supplied by the Monsanto Chemical Company, of St. Louis, Missouri and Eli Lilly and Company, Indianapolis, Indiana.

Addendum

This case has been referred to in an article on the use of TEPP in the treatment of myasthenia gravis. (Stone, C. T., and Rider, J. A.: Treatment of myasthenia gravis, J. A. M. A. **141**: 107–111, 1949.)

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AUREOMYCIN * TREATMENT OF RECURRENT CHOLANGITIS WITH LIVER ABSCESSES DUE TO *BACTEROIDES FUNDULIFORMIS* †

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THE purpose of this report is to present an unusual case in which aureomycin was effective against an infection with *Bacteroides funduliformis* where other antibiotics failed. This patient is of particular interest in that she had varying degrees of jaundice for four years and 13 known hepatobiliary operations within a five-year period.

CASE REPORT

A 33 year old white married female was admitted to Monmouth Memorial Hospital, Long Branch, New Jersey, on October 27, 1948. She had been ill for three days with nonradiating colicky upper abdominal pains associated with chills and fever. The patient noted that simultaneously her stools had become lighter in color and her urine darker. Her illness dates from October, 1943, and includes many hospitalizations. These are summarized in chart 1. As is evident from the chart, the patient had received very large doses of penicillin, sulfonamides and streptomycin without significant improvement.

Physical examination at this time revealed a jaundiced white female who appeared acutely ill. Salient findings included evidence of marked weight loss; the patient's weight was now 110 pounds, a loss of 100 pounds since cholecystectomy in 1943. Her temperature was 101.6° F.; blood pressure, 120 mm. Hg systolic and 70 mm. diastolic;

* Aureomycin was generously supplied by the Lederle Laboratories Division, American Cyanamid Company, Stanton M. Hardy, M.D., Medical Director.
† Received for publication July 9, 1949.
From the Department of Medicine, New York Medical College (Dr. Linn J. Boyd, Director), the Research Unit, Metropolitan Hospital (Dr. Thomas McGavack, Director), New York City, and the Department of Medicine, Monmouth Memorial Hospital (Dr. Frank Altschul, Director), Long Branch, New Jersey.
‡ Deceased.

CHART I

Previous Hospital Admissions

Date	Hospital	Manifestations	Therapy	Results
1943	Fitkin Memorial Hospital, Neptune, N. J.	Substernal pressure and jaundice	Cholecystectomy	Continued to have daily temperature elevation
1943	Fitkin Memorial Hospital	Pleuritic pain and temperature elevation	Thoracentesis, probably subdiaphragmatic. Culture was "*B. coli* and staphylococci." Sulfamerazine, 6–8 gm. daily. Sulfadiazine, 8 gm. daily	Very little effect on temperature
1943	Fitkin Memorial Hospital	Right upper quadrant pain plus temperature elevation	Incision and drainage of subphrenic abscess. Sulfamerazine, 4–6 gm. daily	Very little effect on temperature
1944	Fitkin Memorial Hospital	Right upper quadrant pain plus temperature elevation	Incision and drainage of subphrenic abscess. Sulfamerazine, 4–6 gm. daily	Very little effect on temperature
1944	Fitkin Memorial Hospital	Right upper quadrant pain plus temperature elevation	Incision and drainage of subphrenic abscess. Sulfadiazine, 4–6 gm. daily	Temperature normal for six consecutive days
1944	Fitkin Memorial Hospital	Right upper quadrant pain plus temperature elevation	Incision and drainage of subphrenic abscess, which was irrigated with 200,000 units of penicillin	Temperature normal for 14 consecutive days
1944	Fitkin Memorial Hospital	Right upper quadrant pain plus temperature elevation	Incision and drainage of subphrenic abscess. Sulfadiazine, 6–10 gm. daily. Penicillin, 80,000 units I.M. daily	No effect on temperature
1944	Fitkin Memorial Hospital	Right upper quadrant pain, temperature elevation and jaundice	Incision and drainage of subphrenic abscess. Sulfadiazine 6–8 gm. daily	Temperature normal for three consecutive days
1944	Fitkin Memorial Hospital	Right upper quadrant pain, temperature elevation and jaundice	Incision and drainage of subphrenic abscess. Sulfadiazine, 6–8 gm. daily	Temperature normal for three consecutive days
1945	Hahemann Hospital, Philadelphia, Pa.	Right upper quadrant pain, temperature elevation and jaundice	Thoracotomy	Continued to have elevations of temperature
1945	Fitkin Memorial Hospital	Right upper quadrant pain, temperature elevation and jaundice	Transduodenal choledocholithotomy with removal of small stones from the common bile duct. Penicillin, 240,000 units I.M. daily	Very little effect on temperature elevations

CHART I—*Continued*

Date	Hospital	Manifestations	Therapy	Results
1946	Hospital for Joint Diseases, New York City	Right upper quadrant pain, temperature elevation and jaundice	The right hepatic duct was anastomosed to the proximal portion of the jejunum over a vitallium tube, which the patient subsequently passed. Unable to find trace of the common bile duct or of the left hepatic duct	Very little effect on temperature elevations
1947	Fitkin Memorial Hospital	Right upper quadrant pain, temperature elevation and jaundice	Penicillin, 240,000 units I.M. daily	Temperature normal for three consecutive days
1947	Fitkin Memorial Hospital	Right upper quadrant pain, temperature elevation and jaundice	Penicillin, 240,000 units I.M. daily	Very little effect on temperature elevations
1947	Monmouth Memorial Hospital, Long Branch, N. J.	Right upper quadrant pain, temperature elevation and jaundice	Penicillin, 400,000–500,000 units I.M. daily. Streptomycin, 2 gm. daily. Sulfadiazine, 4–6 gm. daily	Temperature normal for five consecutive days
1947	Mount Sinai Hospital, New York City	Right upper quadrant pain, temperature elevation and jaundice	The distal end of the jejunum was closed and the proximal end was then implanted end-to-side into the jejunum about 10 inches below the point of the junction of the jejunum with the right hepatic duct. Unable to find trace of the common bile duct or left hepatic duct	Continued to have elevations of temperature
1948	Monmouth Memorial Hospital	Right upper quadrant pain, temperature elevation and jaundice	Penicillin, 1,200,000 units I.M. daily. Streptomycin, 2 gm. daily. Sulfathalidine, 2 gm. daily	Temperature normal for five consecutive days
1948	Monmouth Memorial Hospital	Right upper quadrant pain, temperature elevation and jaundice	Penicillin, 400,000 units I.M. daily. Streptomycin, 2 gm. daily. Sulfadiazine, 6 gm. daily	Temperature normal for seven consecutive days
1948	Research Unit, Metropolitan Hospital, New York Medical College	Right upper quadrant pain, temperature elevation and jaundice	Penicillin, 1,400,000 units I.M. daily. Decholin, 10 c.c. I.V. daily	Temperature normal for five consecutive days

pulse, 120 per minute. Two operative scars were observed in the right upper quadrant, one in the right lower quadrant, and another in the right lower chest laterally. There was abdominal tenderness, most marked in the right upper quadrant. The liver was felt three fingerbreadths below the right costal margin. The spleen could not be palpated.

The patient received 100,000 units of penicillin intramuscularly every three hours. For relief of pain, codeine, aspirin and demerol were given. Vitamins and a high caloric diet were also prescribed. A daily elevation of temperature from 100 to 103.8° F. continued, with an occasional chill.

Penicillin was discontinued on November 9, and the patient began at this time to receive 50 mg. aureomycin orally every four hours. Within 48 hours the patient's temperature dropped below 99° F. After a week of treatment, abdominal tenderness disappeared, the appetite increased and the patient felt much improved. Because of lack of supply, however, it was necessary to discontinue the use of aureomycin after that first week. Within 24 hours of discontinuance the temperature rose to 100.6° F. and by the next day had reached 104° F.

The house staff of the hospital resumed the use of penicillin, ordering as much as 250,000 units in saline intramuscularly every three hours, plus 300,000 units intramuscularly in oil every evening. Since there was very little effect, 3 gm. of dihydrostreptomycin was ordered in addition. This régime was abandoned and sulfathalidine was given, also with very little effect on the clinical course.

Before re-instituting aureomycin therapy, the authors decided to investigate this case more fully. Three blood cultures, three urine cultures and three stool cultures were negative. An upper gastrointestinal series revealed no organic lesion in the stomach or small bowel. In the roentgen-ray series the radiologist * was unable to see any evidence of previous operations. The mucosal pattern of the small bowel appeared normal, although there was a slight delay in the passage of barium in the lower loops. A chest plate was essentially negative. A Levine tube was passed into the stomach under as sterile conditions as possible and fluid was withdrawn (see chart 2). Under fluoroscopic visualization the tube was next passed through the pylorus.

CHART II

Gastric, Duodenal and Jejunal Washings

Washings	Free HCl	Total HCl	Amylase	Tryptic Activity	Bile
Gastric	12.5°	30.5°			
Stimulation at sphincter of Oddi	Neg.	18°	20 units	Between 2 and 10	Neg.
Stimulation at anastomoses in jejunum	7°	22.5°	Neg.	Less than 0.25	Pos.

Around the area of the sphincter of Oddi, the patient was stimulated twice with 75 c.c. of 33 per cent magnesium sulfate. Aspirations were clear, so the tube was passed to the jejunum at the approximate area of anastomosis. Magnesium sulfate and olive oil were used as stimulants. Yellow aspirations were withdrawn from which cultures were made. An attempt to instill barium so as to outline the biliary tree was unsuccessful, for the patient pulled out the tube after nine hours of intubation.

On January 14, 1949, following these studies, 250 mg. of aureomycin every four hours around the clock was begun. For supplementation, the patient received orally choline chloride, methionine and ascorbic acid. Vitamin B complex and crude liver

* Dr. William G. Herrman.

were given parenterally. Within 24 hours the temperature had dropped to 99° F. During the 16 days that aureomycin was administered, the temperature never rose above 99.8° F., abdominal tenderness disappeared, and the patient again felt clinically improved. Occasionally a slight nausea occurred, but this did not affect the patient's appetite, which had increased tremendously.

One day after aureomycin was discontinued, the temperature rose to 101° F., and in subsequent days to 102° F. Simultaneously, malaise, abdominal tenderness and anorexia returned. Accordingly, on February 6, the patient again was started on aureomycin, this time receiving 500 mg. every four hours around the clock. As a result, the temperature came down to 99° F. and remained there while the patient improved clinically. After a few days the dosage was lowered to 250 mg. every four hours, and on February 23 the dosage was further lowered to 250 mg. three times daily. With this reduction of dosage, chills and temperature recurred, reaching 103.8° F. by the third day. The patient complained of squeezing pains across the entire lower chest, radiating to the midback. Marked tenderness was noted below the left costal margin and in both costovertebral angles, especially on the right. The patient had slight dysuria and frequency of urination, but no color change in the stools or urine. There were no dyspnea, coughing or vomiting, though some nausea occurred. Serum amylase on February 26 was 65 units (Somogyi). Electrocardiogram and chest roentgenogram were normal. Urine was essentially negative. It was felt that the most likely diagnosis was a rupture of a small intrahepatic abscess.

Aureomycin treatment was stepped up to 500 mg. every four hours, with a temperature drop to 99° F. within 24 hours. Later the dosage was reduced to 250 mg. every

CHART III

Liver Function Tests*

Date	I.I.	V.D.B.	T.T.	P.	Alk.P.	T.C.	F.C.	C.E.	T.S.P.	A.	G.	A/G
8/4/48	100	biph.	4+	4.1	75	270	185	85	9.1	4.1	5	0.8
8/6	41		4+			362	210	152				
8/10	47	pos. immed.	4+	3.8	32.2	322	187	135	9.5	4.1	5.4	0.75
8/17	100	biph.	4+	3.5	24	262	132	130	8.2	4	4.2	0.9
8/24	51	biph.	4+	4	30	340	140	200	8.5	4	4.5	0.9
8/31	104	biph.	4+	4.3	35	290	110	180	8.7	4.9	3.8	1.3
9/7	150	biph.	4+	5	36.6	240	120	120	8.4	3.4	5.0	0.7
9/14	95	biph.	3+	4.2	29	200	87	113	8.3	4.5	3.8	1.2
9/21	42	biph.	3+		30	328	75	253	9.0	4.9	4.1	1.2
9/28	115	biph.	3+	4.4	40.5	326	90	236	8.7	4.9	3.8	1.3
2/2/49	80	biph.	3+		50.2	388	208	180	8.0	3.0	5.0	0.6
2/9	50	pos.	1+		47	233	130	103	7.0	3.5	3.5	1.0
2/16	35	pos.	1+		13.2	308	210	98	6.3	3.9	2.4	1.6
2/23	38	pos.	1+		15.1	336	150	186	7.6	4.6	3.0	1.5
2/30	30	pos.	2+		12.5	306	125	181	6.7	3.8	2.9	1.3
3/10	30	pos.	2+		37.3	390	240	150	6.7	3.8	2.9	1.3
3/24	23	pos.	1+		27.0	410	150	260	7.0	4.1	2.9	1.4
3/31	23	pos.	neg.	4.5	16.3	272	102	170	7.0	4.2	2.8	1.5

Key to Abbreviations

I.I.—Icterus index
V.D.B.—van den Bergh
T.T.—Thymol turbidity
P.—Phosphorus
Alk.P.—Alkaline phosphatase (Bodansky units)
T.C.—Total cholesterol
F.C.—Free cholesterol
C.E.—Cholesterol esters
T.S.P.—Total serum proteins
A.—Albumin
G.—Globulin
A/G—Albumin globulin ratio
biph.—biphasic

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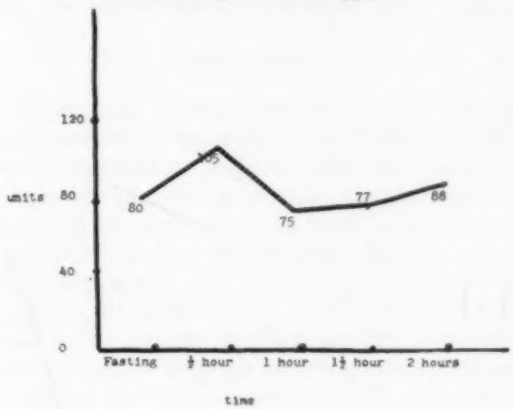
four hours. This time with reduction, the temperature did not rise above 100° F. rectally, and improvement continued in appetite, clinical picture and liver function tests (chart 3). (Chart 4 indicates that the patient probably had no pancreatic involvement at this time.) Right costovertebral angle tenderness disappeared, and abdominal and left costovertebral angle tenderness lessened (the latter was absent on bending) but remained for two weeks.

Because of lack of supply, the patient was without aureomycin again for three days, with a resultant chill and temperature elevation. Serum amylase at this time was 75 units. No change in color of stools or urine occurred, although there were slight nausea and some sharp pains below the left costal margin going through to the back and to the epigastrium. With resumption of 250 mg. aureomycin every four hours, the temperature became normal and abdominal tenderness and pain subsided.

This patient was discharged from the hospital on April 8, 1949, with a maintenance dosage of 250 mg. aureomycin every four hours. Six days later she was seen

CHART IV

Serum Amylase (Somogyi)



in the office of S. H. R. with no temperature elevation and no symptoms. Her weight on this occasion was 127 pounds, a weight gain of 17 pounds since the inception of aureomycin therapy.

On April 21, the patient developed an itching maculopapular rash. Associated with this skin eruption were nausea, vomiting, diarrhea and swelling of knees, ankles and all finger joints. No redness of the skin overlying the joints occurred. At this time temperature was 101° F. She had received no medication other than aureomycin. Three days after receiving benadryl, 50 mg. three times daily, all of her symptoms subsided. Examination on May 4 revealed a slight increase in her icterus but no abdominal tenderness or joint swelling. Her weight was 128 pounds. She was again seen at the office on May 11, at which time she stated that she had not felt so well in several years and that she had gained more weight. Temperature remained normal throughout the week. The patient did not have any symptoms referable to her abdomen or joints.

Bacteriology: Washings from jejunum were inoculated into thioglycolate broth. After five days' incubation a foul odor was noticed which simulated that of *B. coli* cultures. Microscopically, rather smooth gram-negative rods were seen. Subcultures proved to be negative for any of the typhoid-dysentery-colon groups.

Fresh subcultures were made by inoculating thioglycolate broth and streaking

blood plates, which were incubated simultaneously in a Brewer's jar for a period of two weeks. Two days prior to examination of the Brewer's anaerobic jar preparation, an inulin broth was inoculated from the original stock culture. There was abundant growth, with acid and gas formation. Smears were made and organisms appeared to have morphology similar to those of original culture.

At this time slides were made from the anaerobic cultures which had abundant growth. Examination of these slides revealed highly pleomorphic filamentous bacilli with metachromatic granules. It was the opinion of the Department of Bacteriology * that they were working with organisms of the genus *Bacteroides*, and by careful comparative study it was concluded to be *Bacteroides funduliformis*. The morphology and characteristics of the culture were similar to that strain.

Agglutination tests were made employing fresh patient's serum with the 48 hour inulin broth culture. The results were negative in all dilutions. At the same time, agglutinations were set up employing fresh patient's serum with the two week old anaerobic culture, the one in which metachromatic granules were demonstrated. Agglutinations were strongly positive up to and including 1 : 320 dilution of serum.

An aureomycin sensitivity test was conducted by the test tube method. The report was positive, indicating that 1 c.c. of active broth culture was inhibited by 0.025 mg. of aureomycin.

Comment

The only reported case in any way allied to our present study was that of Finland et al.[1] In this article, aureomycin was administered to a patient having a colon bacillemia associated with jaundice, an enlarged liver and an epigastric mass. Although this case was improving clinically during treatment, an intestinal hemorrhage resulted in death and no autopsy could be obtained.

It is felt that the etiologic agent of our patient's infection is the *Bacteroides funduliformis* for the following reasons: first, the agglutination of the patient's serum with the culture in dilution of 1 :320; second, the sensitivity of the organism to aureomycin in vitro, and the marked clinical improvement with moderate dosages. This organism was probably the same as the one cultured from the original subphrenic abscess. It had a colon odor, and the first impression on examination of the slide was *B. coli*. During the war years, with the shortage of laboratory help, this organism may not have been subcultured.

Aureomycin was effective where other antibiotics failed. Despite two biliary anastomotic operations and other antibiotics, the patient's symptoms continued and were not abated until she received aureomycin. Three different times over a four month period the drug was discontinued, with a return of abdominal pain and an elevation of her temperature within a 48 hour period. On resuming treatment, both temperature and pain subsided within 24 hours. We saw no apparent resistance to the drug during this prolonged administration.

In addition to nausea and looseness of the stools, listed by others as toxic symptoms, we noticed another reaction which was even more severe in this patient. After almost four months of the drug therapy the patient developed a reaction believed to be allergic, consisting of swelling of the joints of her hands, knees and ankles, plus a generalized maculopapular rash and diarrhea. Symptoms responded well to benadryl, and the patient is receiving both benadryl and aureomycin at the present time.

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Summary

We have described a case of recurrent cholangitis with probable liver abscesses, which showed marked clinical and laboratory responses to aureomycin where other antibiotics failed. No resistance to the aureomycin has occurred, although the drug has been administered continuously for a four month period. The only serious toxic effect was a swelling of several joints and a maculopapular rash, all of which responded well to benadryl.

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EDITORIAL

THE SURGICAL TREATMENT OF MITRAL STENOSIS

More than 50 years ago Samways [1] anticipated that "with the progress of cardiac surgery some of the severest cases of mitral stenosis will be relieved by slightly notching the mitral orifice." A few years later Lauder Brunton [2] conducted some investigations on appropriate technics and suggested that relief might be obtained by surgical division of the diseased valve. This excited a storm of letters pro and con, and the *Lancet* [3] published an editorial strongly critical of Lauder Brunton in which were raised all the theoretical disadvantages which are repeated today. Sir James McKenzie is said to have considered the proposal and to have decided to "leave the troubles and the dangers for others." [4] However, in the two following decades several procedures were devised and tested for dividing valve leaflets in animals including the development of an instrument which permitted a view of the portion of the valve to be incised.[5, 6, 7, 8, 9] Interest in these technics was shared by surgeons looking to the operative relief of obstructive valvular disease, and by physiologists or pathologists studying the dynamic effects of experimental mitral insufficiency.[10, 11] The aim of both was to enlarge the mitral orifice by excision of a portion of the margin or body of a valve leaflet.

With the progress of thoracic surgery Cutler and others applied this technic in the early 1920's to mitral stenosis in man.[9, 12, 13, 14] In nine patients a portion of a cusp (usually the anterior) was incised by means of an instrument inserted in seven cases through the wall of the left ventricle and in two [9, 14] through the left auricular appendix. One patient survived four

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[2] Brunton, L.: Surgical operations for mitral stenosis, Lancet **1**: 352, 1902.
[3] Editorial: Lancet **1**: 461, 1902.
[4] McKenzie, J.: Quoted by Cutler, Levine and Beck.[12]
[5] Haecker, R.: Experimentelle Studien zur Pathologie und Chirurgie des Herzens, Arch. f. klin. Chir. **84**: 1035, 1907.
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and a half years though her activities were severely restricted and frequent readmissions to the hospital were necessary. Of the remaining eight, none lived for a week and the majority died within a few hours.[15] In another case Souttar[16] dilated the mitral orifice with a finger introduced through the left auricular appendix. This patient was reported to be alive and improved six years later. Review of the reported fatalities reveals that many of the patients were far advanced in congestive heart failure, a fact now known in itself to impair the outlook for satisfactory operative result. However, after the disappointing consequences of these attempts, the surgical treatment of patients with mitral stenosis was abandoned for nearly 20 years.

In the meantime other events added impetus to the attack on the problem: improvements in anesthesia, the experience during the war in the field of cardiac surgery, and, most important, the control of infection by chemotherapy or antibiotics. Finally the development and application of physiological technics such as cardiac catheterization for estimating the dynamic consequences of mitral obstruction advanced the knowledge of the natural history of this disease, permitting a description of the disability in more or less quantitative terms.

The progress of disability in patients with mitral stenosis is marked by symptoms and signs which arise from engorgement of the pulmonary circulation. The outflow of blood is obstructed at the mitral orifice but inflow is supported by a competent right ventricle. Normally the vascular channels within the lungs are not fully distended by the resting blood flow; with exertion right ventricular output may increase several fold without significant rise in pulmonary artery pressure. With mitral stenosis, on the other hand, the pulmonary vessels are already overfilled; and the pressure in the pulmonary vascular system rises sharply with exercise. Left auricular pressure measured at operation in such patients has been recorded[17] at 30 to 40 mm. Hg (normal 6 mm. Hg). Pulmonary "capillary" pressure * —recorded by occluding with the cardiac catheter a distal branch of the pulmonary artery—has been shown to be high in many cases, reaching the vicinity of 40 mm. Hg mean (normal not over 10 mm. Hg).[18, 19] It is the

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* Although not actually measured in the pulmonary capillary this value is certainly no lower than the capillary pressure.

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critical changes in this pressure with exertion or excitement which precipitate the attacks of pulmonary edema which occur in many cases.

In patients with mitral stenosis who have symptoms of circulatory disability the pulmonary artery pressure has almost invariably been found to be elevated at rest. In its early phases such pulmonary hypertension may be a direct consequence of the barrier at the mitral orifice. In many instances of longstanding disease the pressure in the pulmonary artery may be excessively high, even approaching systemic arterial pressure,[20] and the gradient from arterial to "capillary" pressure augmented,[19] indicating an increase in pulmonary arteriolar resistance. Some degree of peripheral pulmonary vasoconstriction is suggested by the observation that in certain cases of mitral stenosis pulmonary arterial pressure rises with exercise even though right ventricular output does not increase.[20] Probably more significant in the sustained pulmonary hypertension sometimes encountered are the changes in the arterioles and finer pulmonary vessels which have been repeatedly described in fatal cases [21, 22, 23, 24] with right heart failure.

Dyspnea first noted upon exertion is commonly accompanied by cough. In the early phases of disability the vital capacity is not strikingly reduced but exertion provokes hyperventilation, probably due to reflexes from the engorged, turgid lung. Congestion proceeds from the distended pulmonary veins backward to force open and to distend all available pulmonary capillaries and, as the pressure in these rises, the elasticity of the lung diminishes. Pericapillary transudate, which results when intracapillary pressure exceeds the oncotic pressure of the blood, contributes to this and in addition impedes the local diffusion of gases. *Cough* or clinical manifestations of pulmonary edema after effort are evidently also consequences of effusion of fluid from blood through the capillary wall.

Hemoptysis: During attacks of acute pulmonary edema blood cells may penetrate the alveoli by diapedesis and the sputum may be pink and frothy; with this, dyspnea is severe and cough may be violent. In the presence of auricular fibrillation emboli may pass to the lung from the right auricle, or, with chronic passive congestion, local thrombosis of lung vessels may occur; the sputum may then be stained with blood, usually dark in color, or may contain clots.

Of more critical importance are the attacks of frank hemoptysis in which bright red blood wells up in the throat from the trachea without preceding

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or associated breathlessness. Rarely this may be precipitated by an attack of severe coughing, but more frequently the other symptoms of pulmonary congestion are conspicuously lacking at the time of the bleeding. Such profuse hemoptyses evidently arise from varicose enlargement of bronchial veins [25] which constitute collateral channels between the pulmonary and systemic venous systems. Normally, except for a limited area about the hilum, all the blood distributed to the bronchial tree is returned via branches of the pulmonary veins.[26] With mitral obstruction the high pressure within the left auricle is transmitted to these latter vessels, evidently provoking back flow through dilated collateral channels which, communicating with veins in the larger bronchi, empty into the azygos system. Sudden or considerable rise in pulmonary venous pressure may rupture such a bronchial varix with consequent hemorrhage.

Right Heart Failure: Although the systolic and, less commonly, the diastolic pressure in the right ventricle may be elevated at rest in cases of mitral stenosis, unless the normal sequence of ventricular contractions gives place to total irregularity with the onset of auricular fibrillation, or until the sustained burden of pulmonary hypertension becomes overwhelming, systemic venous congestion does not develop. Indeed the competence of a strong right ventricle in discharging its contents into the already distended vessels in the lungs is a basic cause of the disabling engorgement of the pulmonary circulation. Rise of systemic venous pressure and enlargement of the liver indicate intolerable right heart strain.

With improved means for estimating circulatory disability and for describing the changes consequent upon relief of mitral obstruction, active interest in the surgical treatment of mitral stenosis revived. The causes of past failure were studied and new technics were tested. Particular consideration was given to the adverse circulatory effects of the mitral insufficiency which usually resulted from the methods previously employed, and to the hazards of entering the heart through the thick ventricular muscle. When Powers [27] produced mitral stenosis in dogs by electrocoagulation of the mitral valve followed by intravenous inoculation with *Streptococcus viridans* and subsequently performed "partial valvulectomy" by the technic of Cutler, the animals all died within a few days with acute cardiac failure. Attention was therefore directed at reducing obstruction during diastole of the ventricle with the maximum improvement of valvular function during ventricular systole. It was proposed that if the fused valve leaflets could be separated by cutting along the former line of closure (commissure) this purpose might be accomplished. Interest was renewed in Souttar's ap-

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proach to the stenosed mitral orifice through the left auricular appendage, and improved instruments were devised for cutting the valve.[28, 29, 30]

As a result the surgical treatment of mitral stenosis was resumed by several groups soon after the end of the war. Bailey [31] and his colleagues began a series of operations now numbering over 200, cutting the valves apart at the commissures with a specially designed knife attached to the gloved finger and introduced through the left auricle. Harken has operated on nearly 100 cases incising the valves at the commissures in a large proportion. Brock [32] and Blalock [33] have held to the technic of tearing the valves apart by pressure of the finger, a method also practiced in some cases by Harken and by others. Altogether several hundred patients have undergone operation for mitral obstruction during the last five years in various clinics in this country and abroad.

Contemporaneously with the interest in methods for relieving obstruction at the mitral valve attention was directed to operative means of shunting blood from the inflated left auricle and the engorged pulmonary venous system into the more capacious systemic veins. In describing the syndrome which bears his name (mitral stenosis with interauricular septal defect) Lutembacher [34] had presented the case of a woman who lived to the age of 61 and had borne seven children. Others [35, 36] emphasized the relatively favorable course of these patients, particularly their freedom from attacks of acute pulmonary edema or hemoptyses. Without describing how it might be accomplished, Jarotsky [37] had proposed the creation of a defect in the interauricular septum by surgical means. Harken and co-workers [29] after studies of the circulatory disability in a series of patients, suggested that this procedure was appropriate in the cases in which mitral regurgitation predominated over mitral stenosis, and performed the operation with improvement in some patients.

During the same period Bland and Sweet [17] conceived the idea of creating an extra-cardiac venous shunt to minimize the consequences of mitral

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stenosis and designed a procedure to create a vent from the overfilled pulmonary veins by anastomosing the right inferior pulmonary vein to the azygos vein. At about the same time Swan [38] was developing a technic for pulmonary-azygos venous anastomosis in the dog. This operation was performed for the first time in man by Sweet in March, 1948,[39] and has since been applied with considerable relief to the patient in a number of instances.

Indications and Contraindications: The symptoms and signs of engorgement of the pulmonary circulation which have been described above constitute the indications for surgical treatment. However, since a significant number of patients with mitral stenosis live to advanced age without handicap it scarcely seems advisable to intervene by surgical means in every case in which this valve lesion is discovered. But, except in the presence of distinct contraindications, operation should be considered as soon as progressive symptoms of disability appear.

The results so far reported indicate that the chances of striking benefit diminish as the duration of symptoms lengthens. When pulmonary vascular resistance becomes fixed, or when right heart failure persists despite supportive measures, relief is scarcely to be expected and, indeed, the operative mortality is forbiddingly high. There are certain other obvious contraindications to surgical treatment of mitral obstruction. In the presence of active rheumatic carditis with elevated sedimentation rate, fever or leukocytosis, or with bacterial endocarditis, the danger of exacerbating the disease is too real to be risked. Auricular fibrillation does not in itself interdict operation, though when it has been established for months or more it may very genuinely add to the hazard by fostering embolism from mural thrombi. This has appeared as a postoperative complication in 3 to 5 per cent of cases so treated. There is no certain means to distinguish thrombus in the auricle before operation but history of recent embolism should dictate caution.

"Pure" mitral stenosis probably occurs in less than 10 per cent of cases of rheumatic heart disease. Often the lesion is combined with a defect which prevents mitral closure during ventricular systole. In such cases there is a prominent systolic murmur at the apex, the left auricle frequently is enlarged and occasionally dilatation of the auricle with ventricular systole may be observed at fluoroscopy. Enlargement of the left ventricle is more common when stenosis and insufficiency are combined than with mitral stenosis alone. If significant mitral insufficiency accompanies stenosis surgical enlargement of the orifice is likely only to enhance regurgitation.

Experience with the results of mitral valvulotomy in the presence of other valve lesions is so far limited. However, there is sound basis in

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theory for the belief that with obstruction of any significant degree at the aortic orifice relief of mitral obstruction would probably lead to serious mitral regurgitation and to critical reduction in left ventricular output.

Results: Because this is a relatively recent development the longterm results in large numbers of patients with mitral stenosis treated by surgery and followed for several years have not yet been published. Over 200 cases were reported at the International Cardiological Congress (Paris) in September, 1950. Additional series numbering altogether nearly 300 patients were described at the Scientific Session of the American Heart Association in June, 1951, by Janton, Bailey, Harken, Dexter, and others. Other smaller groups of cases have been recorded.[29, 30, 31, 32, 33, 40]

Operative mortality is 12 per cent or less depending upon selection of cases. Relief is dramatic in some instances, and great improvement is accomplished in well over half the patients. In many others orthopnea disappears and dyspnea lessens; the acute attacks of pulmonary edema become infrequent and hemoptyses have not recurred. In only 5 per cent of the cases has it not proved possible to enlarge the valve opening; these are the instances in which the chordae tendineae have contributed to producing a funnel deformity drawing the leaflets into the ventricle beyond the effective reach of knife or dilating finger.

Physiological studies after operation have not revealed complete restitution of the pulmonary circulation to normal; pulmonary arterial pressure, though often diminished, has usually remained above normal values. However, the "capillary" pressure has been shown to fall [33, 40]; and it is evident that after operation this does not rise as high or as dangerously with effort or excitement. Finally the work of the right ventricle against pressure is measurably reduced.[20, 33, 40] Apparently in the majority of cases the barrier at the mitral orifice has been so opened by the operative procedure that increase in pulmonary blood flow can be accomplished upon exertion without stasis or engorgement of critical degree.

As experience accumulates the selection of cases may be expected to become easier and more certain. At present it appears established that the early phases of disability yield most completely to operation. Much remains for study but even so early in the history of modern mitral surgery Samways's prediction is being fulfilled and relief for many of those afflicted with mitral obstruction seems assured.

E. Cowles Andrus

[40] Gorlin, R., Dexter, L., and Harken, L.: Circulatory changes in mitral stenosis following valvuloplasty, J. Clin. Investigation **30**: 643, 1951.

REVIEWS

The Kidney: Structure and Function in Health and Disease. By HOMER W. SMITH, A.B., Sc.D., M.S. 1049 pages; 15 × 23 cm. Oxford University Press, New York. 1951. Price, $12.50.

With its abundant wealth of technical physiology this is a terrifying book to the humble clinician.

The text is divided into four parts. The first deals with such subjects as anatomy, measurement of the filtration rate, clearances involving tubular reabsorption and excretion, and the reliability of inulin as a measure of glomerular filtration. The second part contains chapters on the antidiuretic hormone and the excretion of water, the excretion of sodium and other strong electrolytes, the adrenal cortex and Addison's disease, and acid-base equilibria in plasma and urine. Part III is devoted to such topics as the control of the renal circulation, hormones and vitamins related to renal function, the comparative physiology of the kidney, and renal hemodynamics.

The final part is far more clinical in scope and in turn discusses limitations of clearance methods during disturbed renal function, primary disturbances of salt and water balance, disturbances of renal function in non-renal disease, chronic congestive heart failure, essential hypertension, acute renal failure related to traumatic and toxic injuries, the juxtamedullary circulation, diseases of the kidney and urinary tract, and diuretics.

The book is excellently written and is a masterpiece of collation. No pains have been spared to make it marvellously complete. This is the work to consult if, for instance, you wish to know how urea is handled by the elasmobranch kidney, or what the xylose U/P ratio is in the sculpin, *Myoxocephalus octodecimspinosus.* Apart from its store of such physiological arcana, the book contains many sections (notably in Part IV) which are of immediate interest and value to the practising physician; among these may be mentioned the excellent discussions on lower nephron nephrosis, on diuretics, and on the current concepts of the mechanisms involved in salt and water retention in congestive failure. The text is fully documented with a bibliography of nearly 2,300 references.

The title of this book is somewhat misleading, for *structural* changes receive only minor treatment, and "health and disease" would not seem to imply that major attention is paid to experimental physiology. In a sentence the book may best be appraised as an exhaustive and exemplary treatise on normal and abnormal renal physiology.

H. J. L. M.

Sterility and Impaired Fertility: Pathogenesis, Investigation and Treatment. By CEDRIC LANE-ROBERTS, C.V.O., M.S., F.R.C.S., F.R.C.O.G., ALBERT SHARMAN, M.D., Ph.D., M.R.C.O.G., KENNETH WALKER, M.A., M.B. (Cantab), F.R.C.S., F.I.C.S., B. P. WIESNER, D.Sc., Ph.D., F.R.S.E., and MARY BARTON, M.B., B.S. 400 pages; 22.5 × 14.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1948. Price, $6.50.

The authors, five in number, are specialists in their particular fields. They have attempted to bring together in one volume a very large and controversial subject.

This edition, which is the second, the first being in 1939, has brought up to date, as much as any book can, the newer concepts of this great problem. One believes that these authors have attempted to present to the general practitioner a detailed and voluminous information which should also be very beneficial to the specialist who is interested at all in the problem of sterility and impaired fertility. Certainly they have brought to the fore the knowledge that the male, or husband, plays a definite rôle in

childless marriages. This fact has not been brought to the attention of the public nor to the medical profession as much as it could have been in the past.

The text starts out with a general survey of the problem of sterility, basic definitions which are important if one is to understand the literature; and then goes directly into the study of the male, rather than the female pathology. Regardless of whether one is studying male or female, this book is most helpful. After going into the difficulties one finds in the husband, and the methods of treatment, the text takes up the female portion of the problem. Every phase is discussed and the whys and wherefores are carefully weighed. The methods of treatment are taken up in great detail, with stress being laid on the dangers of estrogenic hormones. Artificial insemination, an important phase of the problem, is covered rather thoroughly.

The appendix, which consists of nine parts, is most helpful in giving forms which are applicable, as well as the practical tests, which are useful in arriving at a conclusion as to the etiological factors in the case of sterility. One portion of the appendix takes up diathermy, which has not apparently gained the popularity in this country that it has in Great Britain. However, it is certainly something that should be considered to a greater extent than it has been in the past.

The references in the bibliography are rather widespread in regard to nationalities, but one feels that possibly the authors overlooked a few of the more important American writings. However, it does not seem to have affected the subject matter of their text.

All in all, this book could be recommended to anyone, whether he is a general practitioner, or specialist, who is interested in the problem of sterility.

E. I. C., Jr.

James Lind: Founder of Nautical Medicine. By Captain Louis H. Roddis, U. S. N. 177 pages; 21.5 × 14 cm. Henry Schuman, Inc., New York. 1951. Price, $3.00.

Paracelsus: Magic into Science. By Henry M. Pachter. 360 pages; 21.5 × 14 cm. Henry Schuman, Inc., New York. 1951. Price, $4.00.

These two recent publications from the Henry Schuman house comprise a valuable contribution to medical biography.

Most of us recall that the citrous cure for scurvy was long ago established in the Royal Navy, and that Englishmen ever since have been known as limeys. Some of us remember Lind's name in connection with this medical milestone. Few of us, however, fully appreciate his place in medical history. Captain Roddis' purpose is to remedy an important gap in medical biography, for he considers Lind's to be one of the greatest names in medicine and in the tale of human progress.

Many of us fail to realize the importance of scurvy in the three centuries between 1500 and 1800 when it took such a fiendish toll of seafaring men—accounting for more than battles, wrecks and all other nautical hazards put together. Lind made the first clear demonstration that citrous fruits were effective in the prevention and treatment of this disease. Among his many other contributions he was first to demonstrate that fresh water could be made from sea water by simple distillation, and the quarantine methods that he founded did much to reduce the incidence of typhus in the Royal Navy.

Much local color is introduced so that it is interesting and easy to visualize the background against which Lind's many-sided work was accomplished. The content makes the text highly readable despite the fact that it is often dully written with considerable unnecessary repetition. And no mariner, ancient or modern, should be guilty of misquoting Coleridge's famous

"Water, water, everywhere,
Nor any drop to drink."

The volume is completed by a full list of Lind's publications—the first to be compiled, a list of source material, and a brief chronological table of events occurring in the 18th century.

The Paracelsian volume is one of contrasts—as any treatise on this subject must inevitably be. The profile of Paracelsus' character is clearly delineated as we follow his restless and quarrelsome odyssey across Europe. Surely no other historical figure ever so consistently placed himself

> "Between the pass and fell incensed points
> Of mighty opposites."

As soon as he arrives at one of his numerous destinations his arrogance and "self-destructive martyr urge" turn the air blue with brawling. He rants and raves against orthodoxy, drinks to excess in the taverns, hobnobs with teamsters and wears filthy clothes. Yet we see shining against this background of contention and squalor a genuine humanistic interest in mankind, an irresistible urge to help the needy, an amazing industry, a passion for truth and a widely acclaimed skill at healing.

The author regards the life of Paracelsus as "a clue to the riddle of the Renaissance." He was a mystic and yet a scientist, rational yet superstitious. In his teachings are the germs of today's psychiatry and chemotherapy, and among his prolific writings are to be found the first treatise on gynecology and the first on an occupational disease.

While the narrative sections must interest all, the rather lengthy discussions of Paracelsus' philosophy and of his place in Renaissance thought are meat for the student of philosophy, but will not hold the attention of the average reader. For him these sections of the scholarly text are tedious, over-detailed, and inclined to repetitiousness.

The book is artistically produced and beautifully illustrated with reproductions, including topical works by Rembrandt, Durer and Holbein. The text is fully documented with bibliographic notes and appendices on various subjects, including magic and alchemy.

These two books, different in all respects except their biographical vein, will be attractive additions to the bookshelf for less technical medical annals.

H. J. L. M.

The American Illustrated Medical Dictionary: A Complete Dictionary of the Terms Used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology and Medical Biography with Their Pronunciation, Derivation, and Definition. 22nd Ed. By W. A. Newman Dorland, A.M., M.D., F.A.C.S. 1736 pages; 25 × 16.5 cm. W. B. Saunders Co., Philadelphia. 1951. Price, $10.00.

The twenty-second edition of Dorland's *Medical Dictionary* appears in new typography and new design, 76 pages greater in length than the preceding edition. In addition to many new scientific terms, new material includes an article on Fundamentals of Medical Etymology by Professor Lloyd W. Daly of the Department of Classical Studies of the University of Pennsylvania, and a table of Modern Drugs and Dosage provided by Dr. Austin Smith, Editor of the *Journal of the American Medical Association,* and based on New and Nonofficial Remedies, published under the direction of the Council on Pharmacy and Chemistry of the American Medical Association. This new edition of the old standby continues to fulfill its purpose "to give its users the most complete coverage possible of the fast-growing medical vocabulary."

M. L. W.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Annual Review of Medicine. Volume 2. WINDSOR C. CUTTING, Editor, Stanford University School of Medicine; HENRY W. NEWMAN, Associate Editor, Stanford University School of Medicine. 485 pages; 23 × 16 cm. 1951. Annual Reviews, Inc., Stanford, California. Price, $6.00.

Chest X-Ray Diagnosis. By MAX RITVO, M.D., Assistant Professor of Radiology, Harvard Medical School, etc. 558 pages; 26.5 × 18 cm. 1951. Lea & Febiger, Philadelphia. Price, $15.00.

Clinical Tropical Medicine. R. B. H. GRADWOHL, M.D., Editor-in-Chief; LUIS BENITEZ SOTO, M.D., and OSCAR FELSENFELD, M.D., Editors. 1,647 pages; 25.5 × 17.5 cm. 1951. The C. V. Mosby Company, St. Louis. Price, $22.50.

Clinical Unipolar Electrocardiography. By BERNARD S. LIPMAN, A.B., M.D., Assistant in Medicine, Emory University School of Medicine, Atlanta, Georgia, and EDWARD MASSIE, A.B., M.D., F.A.C.P., Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. 232 pages; 22.5 × 14.5 cm. 1951. The Year Book Publishers, Inc., Chicago. Price, $5.00.

Collected Papers of The Mayo Clinic and The Mayo Foundation. Volume XLII, 1950. Edited by RICHARD M. HEWITT, B.A., M.A., M.D., A.B. NEVLING, M.D., JOHN R. MINER, B.A., Sc.D., JAMES R. ECKMAN, A.B., M.A., Ph.D., M. KATHARINE SMITH, B.A., CARL M. GAMBILL, A.B., M.D., M.P.H., and FLORENCE SCHMIDT, B.S.E. 812 pages; 24 × 16 cm. 1951. W. B. Saunders Company, Philadelphia. Price, $11.50.

Committee on Growth of the National Research Council: Fifth Annual Report to the American Cancer Society, Inc. 384 pages; 23 × 15 cm. (paper-bound). 1951. Division of Medical Sciences, National Research Council, Washington, D. C. Price: None set; available to limited number of interested people by writing to their state office of American Cancer Society.

The Control of Cross Infection in Hospitals—Medical Research Council Memorandum No. 11 (Revised Edition, 1951). By THE CROSS INFECTION IN HOSPITALS COMMITTEE OF THE MEDICAL RESEARCH COUNCIL. 49 pages; 24.5 × 15 cm. (paper-bound). 1951. His Majesty's Stationery Office, London. Price, 1s. 9d. net.

Diseases of the Endocrine Glands. By LOUIS J. SOFFER, M.D., F.A.C.P., Associate Attending Physician and Head of the Endocrine Research Laboratory and Clinic, The Mount Sinai Hospital, New York City, etc.; with the assistance of J. LESTER GABRILOVE, M.D., Research Assistant, Endocrine Research Laboratory and Clinic, The Mount Sinai Hospital; with the Section on Carbohydrate Metabolism, Hypoglycemia, and Diabetes Mellitus by HENRY DOLGER, M.D., Adjunct Physician for Metabolic Diseases; Physician in Charge of the Diabetic Clinic, The Mount Sinai Hospital; and the Section on the Gonads by ARTHUR R. SOHVAL, M. D., Adjunct Physician, and Member of the Endocrine Research Laboratory and Clinic, The Mount Sinai Hospital. 1,142 pages; 24 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $15.00.

Diseases in Old Age: A clinical and pathological study of 7941 individuals over 61 years of age. By ROBERT T. MONROE, M.D. 407 pages; 22 × 14.5 cm. 1951. Harvard University Press, Cambridge. Price, $5.00.

Expert Committee on Insecticides: Report on the Second Session, Geneva, 4–11 October 1950: World Health Organization Technical Report Series No. 34. 82 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva. Price, 55 cents.

First Report on Institutional Research Grants of the American Cancer Society—July 1949–June 1950. 258 pages; 23 × 15 cm. (paper-bound). 1951. American Cancer Society, New York. Price: Available without cost to limited number of interested people by writing to state office of American Cancer Society.

Heart Disease in Pregnancy. By A. MORGAN JONES, M.Sc., M.B. (Vict.), F.R.C.P. (Lond.), Deputy Director of the Department of Cardiology, Lecturer in Clinical Cardiology and in Applied Physiology, University of Manchester, etc.; with a Foreword by PROFESSOR CRIGHTON BRAMWELL, M.A., M.D., F.R.C.P. 57 pages; 22.5 × 14 cm. 1951. Grune & Stratton, Inc., New York. Price, $1.50.

Hope and Help for the Alcoholic. By HAROLD W. LOVELL, M.D. 215 pages; 21 × 14 cm. 1951. Doubleday & Company, Inc., Garden City, New York. Price, $2.75.

Lehrbuch der Röntgendiagnostik. By H. R. SCHINZ, W. E. BAENSCH, E. FRIEDL and E. UEHLINGER. 1920 pages; 28 × 19.5 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, DM 84.–

Methods in Medical Research. Volume 4. Governing Board: IRVINE H. PAGE, Chairman; A. C. IVY, COLIN M. MACLEOD, CARL F. SCHMIDT, EUGENE A. STEAD and DAVID L. THOMSON. Editor-in-Chief, MAURICE B. VISSCHER. Histochemical Staining Methods, GEORGE GOMORI, Editor; Fluid and Electrolyte Distribution, LOUIS B. FLEXNER, Editor; Studies on Gastrointestinal Pressures, Innervation and Secretions, J. P. QUIGLEY, Editor; Tissue Culture Methods, C. M. POMERAT, Editor. 306 pages; 22.5 × 14 cm. 1951. The Year Book Publishers, Inc., Chicago. Price, $7.00.

Nutrition Fronts in Public Health: Proceedings of the Nutrition Symposium Held at Yale University, November 10, 1950—Nutrition Symposium Series, Number 3. By ICIE G. MACY, BENJAMIN H. ERSHOFF, CLIVE M. MCCAY, ERNST SIMONSON, HOWARD A. SCHNEIDER and LEO T. SAMUELS. 168 pages; 23 × 15 cm. (paper-bound). 1951. The National Vitamin Foundation, Inc., New York. Price, $1.50.

Die Orale Strophanthin-Behandlung. By BERTHOLD KERN. 382 pages; 25 × 16.5 cm. 1951. Ferdinand Enke Verlag, Stuttgart. Price, Gehefter DM 18.–; gebunden DM 21.–

Physical Diagnosis. By RAYMOND W. BRUST, A.B., M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania Medical School; Introduction by TRUMAN G. SCHNABEL, A.B., M.D., F.A.C.P. 294 pages; 22 × 15 cm. 1951. Appleton-Century-Crofts, Inc., New York. Price, $4.50.

Principles of Medical Statistics. 5th ed. By A. BRADFORD HILL, D.Sc., Ph.D., Professor of Medical Statistics in the University of London (London School of

Hygiene and Tropical Medicine), etc. 282 pages; 22 × 14 cm. 1950. Oxford University Press, New York. Price, $3.00.

Proceedings of the Second Clinical ACTH Conference—Volume I, Research; Volume II, Therapeutics. JOHN R. MOTE, M.D., Editor. 531 pages in Volume I; 716 pages in Volume II; 23.5 × 15.5 cm. 1951. The Blakiston Company, Philadelphia. Price, $8.50 per volume.

Report on the Malaria Conference in Equatorial Africa, Held under the Joint Auspices of the World Health Organization and of the Commission for Technical Coöperation in Africa South of the Sahara; World Health Organization Technical Report Series No. 38. 72 pages; 24 × 16 cm. (paper-bound). 1951. World Health Organization, Geneva. Price, 45 cents.

Spatial Vector Electrocardiography: Clinical Electrocardiographic Interpretation. By ROBERT P. GRANT, M.D., and E. HARVEY ESTES, JR., M.D. 149 pages; 21.5 × 14 cm. 1951. The Blakiston Company, Philadelphia. Price, $4.50.

Symposium on Steroids in Experimental and Clinical Practice. Edited for the Committee on Arrangements by ABRAHAM WHITE. 415 pages; 23.5 × 15.5 cm. 1951. The Blakiston Company, Philadelphia. Price, $7.50.

Therapy of Dermatologic Disorders, Including a Guide to Diagnosis and a Dermatologic Pharmacopeia. By SAMUEL M. PECK, B.S., M.D., Dermatologist to the Mount Sinai Hospital, New York City, etc.; and GEORGE KLEIN, M.D., Associate Visiting Dermatologist, Morrisania City Hospital, New York City, etc. 383 pages; 24 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $6.50.

Thyreotoxikosen und Antithyreoidale Substanzen. By HANS WILHELM BANSI. 99 pages; 24 × 17 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 11.40.

Les Xanthomatoses. By A.-L. FROEHLICH. 327 pages; 24 × 16 cm. (paper-bound). 1951. Les Editions "Acta Medica Belgica," Brussels. Price, Frs. Belges 190.-

COLLEGE NEWS NOTES

Regional Meetings, Autumn of 1951—American College of Physicians

The following is the present schedule of regional meetings of the American College of Physicians for the Autumn of 1951. Several others are being organized and the dates and places will be announced later. Ordinarily the programs for the regional meetings are mailed only to the members in the region covered, but members from other regions may obtain copies of any programs, upon request to the Executive Secretary of the College.

Region and City	Date (1951)	Governor(s)	Guest Speaker(s)
North Dakota, Bismarck	September 8	R. B. Radl, M.D.	Howard Wakefield, M.D., Chicago
Western Pennsylvania, Pittsburgh	September 12	C. W. Morton, M.D.	T. Grier Miller, M.D., Philadelphia
Arizona–New Mexico, Phoenix	September 29	Leslie R. Kober, M.D., Chairman Walter I. Werner, M.D.	Dwight L. Wilbur, M.D., San Francisco
Arkansas–Oklahoma, Hot Springs	September 29	A. A. Blair, M.D., Chairman Wann Langston, M.D.	C. C. Sturgis, M.D., Ann Arbor E. R. Loveland, Executive Secretary
Western New York, Saranac Lake	September 29	E. C. Reifenstein, M.D.	M. C. Pincoffs, M.D., Baltimore H. Kurtz Canby, A.C.P. Executive Assistant
Montana-Wyoming, Butte	October 5–6	H. W. Gregg, M.D.	Howard P. Lewis, M.D., Portland
Northwest, Seattle (Ore., Wash., Alta., B. C.)	October 5–6	George H. Anderson, M.D., Chairman Merl L. Margason, M.D. John W. Scott, M.D.	Pending
Midwest, Columbus (Ill., Ind., Iowa, Ky., Mich., Minn., Ohio, Wis.)	October 13	Charles A. Doan, M.D., Chairman J. O. Ritchey, M.D. C. H. Drenckhahn, M.D. Benjamin Wolverton, M.D. J. Murray Kinsman, M.D. Douglas Donald, M.D. Wesley W. Spink, M.D. Karver L. Puestow, M.D.	M. C. Pincoffs, M.D., Baltimore E. R. Loveland, Executive Secretary

REGIONAL MEETINGS, AUTUMN OF 1951—AMERICAN COLLEGE OF PHYSICIANS—*Continued*

Region and City	Date (1951)	Governor(s)	Guest Speaker(s)
NEW ENGLAND, Portland (Conn., Maine, Mass., N. H., R. I., Vt.)	October 20	R. S. Hawkes, M.D., Chairman Thomas P. Murdock, M.D. Chester S. Keefer, M.D. Harry T. French, M.D. Herman A. Lawson, M.D. E. L. Amidon, M.D.	M. C. Pincoffs, M.D., Baltimore
KENTUCKY, Louisville	October 27	J. Murray Kinsman, M.D.	Pending
SOUTHEASTERN, Jacksonville (Ala., Fla., Ga., S. C., Cuba)	November 2–3	W. C. Blake, M.D., Chairman E. Dice Lineberry, M.D. Carter Smith, M.D. Robert Wilson, Jr., M.D. José J. Centurión, M.D.	Edward L. Bortz, M.D., Philadelphia M. C. Pincoffs, M.D., Baltimore
NEW JERSEY, Newark	November 7	E. C. Klein, Jr., M.D.	M. C. Pincoffs, M.D., Baltimore E. R. Loveland, Executive Secretary
MIDSOUTH, New Orleans (La., Miss., Tenn., Tex.)	December 7–8*	Thomas Findley, M.D., Chairman L. J. Clark, Sr., M.D. William C. Chaney, M.D. David W. Carter, Jr., M.D.	Pending

* Pending.

Gift to the College Library of Publications by Members

Dr. Julius Bauer, F.A.C.P., Los Angeles, Calif., recently presented a copy of his book, "Differential Diagnosis of Internal Diseases," published by Grune & Stratton, Inc., to the College Library of Publications by Members.

The College Library of Publications by Members is maintained at College Headquarters. Members frequently present copies of their books to the College, and thus the library has become a living memorial to the member-authors.

New Life Members

The College is gratified to announce that the following Fellows have become Life Members of the American College of Physicians since the publication of the last issue of this journal:

Dr. Fred Nathan Miller, Eugene, Ore.
Dr. Glaister H. Ashley, Denver, Colo.

American Board of Internal Medicine

The Officers of the Board for the year beginning July 1, 1951, are:

Walter L. Palmer, M.D., Chicago, Chairman
William B. Porter, M.D., Richmond, Vice-Chairman
Henry M. Thomas, Jr., M.D., Baltimore, Secretary-Treasurer
William A. Werrell, M.D., Madison, Executive Secretary-Treasurer
Victor W. Logan, M.D., Rochester, N. Y., Librarian

The next written examination of the Board will be given October 15, 1951, at various centers over the country.

A west coast oral examination (Part II) will probably be given during October, 1951, but the exact date will be announced later. An east coast oral examination will probably be given in New York City during December, 1951.

American Academy of General Practice Annual Assemblies

The American Academy of General Practice has designated the following cities and dates for forthcoming Annual Assemblies:

Atlantic City, March 24–27, 1952.
St. Louis, March 23–26, 1953.
Cleveland, March 22–25, 1954.

The 16th Annual Meeting of the Mississippi Valley Medical Society will be held in Peoria, Ill., September 19–21, 1951, under the Presidency of Dr. Ralph McReynolds, F.A.C.P., Quincy. A program for the meeting may be obtained from Dr. Harold Swanberg, Secretary, 209–224 W. C. U. Bldg., Quincy, Ill.

The Conference Committee on Graduate Training in Medicine, consisting of representatives of the Council on Medical Education and Hospitals of the American Medical Association, the American College of Physicians and the American Board of Internal Medicine, met at Atlantic City, June 10, 1951. Those present included Doctors William S. Middleton, F.A.C.P., Chairman, Russell Haden, F.A.C.P., Roy W. Scott, F.A.C.P., Walter L. Palmer, F.A.C.P., LeRoy H. Sloan, F.A.C.P., and

Edward Leveroos. Dr. Alex. M. Burgess, Sr., F.A.C.P., one of the representatives of the American College of Physicians, was absent. Ordinary routine work of the Committee was accomplished, and approval was given to a group of hospitals after due consideration and discussion of recent evaluation by visit and correspondence.

Dr. Middleton resigned as Chairman of the Committee, and Dr. Russell Haden, F.A.C.P., now of Crozet, Va., was elected Chairman. There are two members of the Committee from each of the three agencies, Drs. Sloan and Burgess being the representatives of the American College of Physicians. The Committee is primarily concerned with the inspection and approval of hospitals for residencies and the preservation of high standards of professional service in hospitals.

The Annual Meeting of the West Virginia State Medical Association was held in White Sulphur Springs, July 19–21, under the presidency of Dr. Frank J. Holroyd, F.A.C.P., Princeton. Among the guest speakers were Dr. George E. Burch, F.A.C.P., New Orleans, La., "Water and Electrolyte Balance"; Dr. Arthur R. Colwell, F.A.C.P., Evanston, Ill., "Diagnosis and Treatment of Diabetic Acidosis"; Dr. LeRoy H. Sloan, F.A.C.P., Chicago, Ill., "A Composite Picture of Hypertension"; and Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va., "The Role of the Practitioner in the Management of Asthma."

Medical Film Institute Compiling New Data

The Medical Film Institute of the Association of American Medical Colleges, 2 E. 103rd St., New York 29, N. Y., is compiling data for its third inclusive information service on professional medical films now in active production. This clearing-house service is designed to be of value to producers, sponsors and teachers. The information will be made available in this country and abroad, in semi-annual reports, and in answer to specific inquiries. The service will provide a knowledge of the productions currently under way and will permit avoidance of any duplication which may appear to be undesirable. It will acquaint all users with a fore-knowledge of films which may fit curriculum needs, indicate trends in production, and give a valuable over-all view of medical film work being done in the United States.

The Institute is seeking to obtain precise information regarding new film units now being made as well as changes in production status of films previously reported. The Institute requests assistance in discovering and reporting new films or revisions of old films before September 1, 1951.

Dr. Walter Bauer, F.A.C.P., was recently appointed Jackson Professor of Clinical Medicine at Harvard Medical School and Chief of Medical Services at the Massachusetts General Hospital, Boston. He succeeds Dr. James H. Means, F.A.C.P., who has held both posts since 1923.

Dr. Wesley W. Spink, F.A.C.P., Professor of Medicine at the University of Minnesota Medical School and Consultant on brucellosis for the World Health and the Food and Agricultural Organizations of the United Nations, is spending July and August in England, France, Italy, and Yugoslavia correlating current brucellosis research. Dr. Spink's work is a coöperative health effort on an international basis, designed to bring together information of the various brucellosis research centers for the benefit of each country. Dr. Spink addressed the International Congress of Clinical Pathology in London on July 18.

At the meeting of the American Rheumatism Association at Atlantic City on June 9, Dr. Philip S. Hench, F.A.C.P., and Dr. Edward C. Kendall, Rochester, Minn., were named joint winners of the first Mutual of Omaha $10,000 Dr. C. C. Criss Award for outstanding contributions in the fields of public health and safety, because of their brilliant work in the development and use of cortisone.

The Dr. C. C. Criss Award is awarded to the person or persons residing in the United States, Canada, Alaska or Hawaiian Islands, who, in the opinion of the Board of Judges, makes the greatest contribution to the public health and/or safety each year.

Dr. Emanuel B. Schoenbach, F.A.C.P., as of August 31, 1951, has resigned his position as Associate Professor of Clinical Medicine and Assistant Professor of Medicine at Johns Hopkins University School of Medicine and as Physician at the Johns Hopkins Hospital, and has accepted an appointment as Professor of Medicine at the State University Medical Center at New York City, College of Medicine, and Director of the Medical Services at the Maimonides Hospital of Brooklyn, beginning September 1, 1951.

During the recent Annual Meeting of the California Heart Association, Dr. Anton S. Yuskis (Associate), San Diego, Calif., was elected a member of the Board of Directors for a three-year period.

Dr. Burgess Lee Gordon, F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College of Philadelphia, has been appointed the first full time, paid President of the century-old Woman's Medical College of Philadelphia. Heretofore, the Presidency has been on an honorary, part-time basis without salary. Dr. Gordon's plans include the organization of an industrial health division to make the College and its hospital more useful in the highly industrialized area in which it is located. The present Dean, Marion S. Fay, Ph.D., will continue as head of the faculty.

Dr. Henry E. Hamilton (Associate) was recently promoted to the rank of Assistant Professor in the Department of Internal Medicine by the State University of Iowa College of Medicine.

Dr. Francis J. Braceland, F.A.C.P., has been appointed Psychiatrist-in-Chief of the Institute of Living, Hartford, Conn. Dr. Braceland succeeds Dr. C. Charles Burlingame, F.A.C.P., who died in July, 1950. Dr. Braceland was formerly Professor of Psychiatry at the University of Minnesota (Mayo Foundation), and Consultant in Psychiatry at the Mayo Clinic, Rochester, Minn.

Dr. Hyman I. Goldstein (Associate), Camden, N. J., was recently elected Lifetime Medical Historian of the New Jersey Gastro-enterological Society. Dr. Goldstein was also elected Honorary Member of the Italian Gastro-enterological Society of Rome.

Dr. Edwin P. Jordan, F.A.C.P., Cleveland, Ohio, was recently appointed Executive Director of the American Association of Medical Clinics. Among Dr. Jordan's duties will be the development of a program of graduate medical education in private medical clinics equipped for such activity.

Dr. Jacob C. Geiger, F.A.C.P., San Francisco, Calif., was recently honored by His Royal Majesty King Frederik IX of Denmark, through the Royal Danish Ambassador in Washington and the Royal Danish Consul in San Francisco, with the Honorary Knighthood of the Royal Order of Dannebrog. This Honorary Knighthood was accompanied by the following citation:

> "For distinguished service to the Royal Kingdom of Denmark, and its citizens in San Francisco, and for public health work of international significance for the mutual benefit of mankind everywhere."

Dr. Clarence A. Smith, F.A.C.P., Seattle, Wash., after nearly 50 years as Editor of *Northwest Medicine*, has recently retired at the age of 90, although nominally he remains one of the Editors of that Journal.

Dr. Smith was born in 1861 and graduated from Columbia University College of Physicians and Surgeons in 1887. He has been a Fellow of the American College of Physicians since 1922.

Dr. Francis G. Blake, F.A.C.P., Sterling Professor of Medicine at Yale University School of Medicine, has been appointed Scientific Director, Medical Research and Development Board, Office of the Army Surgeon General. Dr. Blake recently resigned from the chairmanship of the Committee on Medical Sciences, Research and Development Board, Department of Defense, which position he had held since 1948.

Rear Admiral John Harper (MC), U. S. Navy, F.A.C.P., was retired by the U. S. Navy on June 30, after 36 years of active duty. Admiral Harper's most recent assignment was as District Medical Officer of the Third Naval District with headquarters in New York, N. Y. His new home address is 4202 Yuma St., N.W., Washington 16, D. C.

Dr. John Minor, F.A.C.P., Washington, D. C., President of the American Clinical and Climatological Association, was recently elected a Member of the American Board of Internal Medicine.

Dr. Charles A. R. Connor, F.A.C.P., resigned as Medical Director of the American Heart Association on June 30, 1951, and has resumed the practice of medicine at 485 Park Ave., New York 22, N. Y.

OBITUARIES

COLONEL CHARLES FRANKLIN CRAIG (MC), USA, RET'D

Colonel Charles Franklin Craig, M.A., M.D., Sc.D., F.A.C.P., a retired Officer in the Medical Corps of the U. S. Army, died at San Antonio, Tex., on December 9, 1950.

He was born in Danbury, Conn., July 4, 1872. He graduated from Yale University School of Medicine in 1894. He became a Medical Officer in the Army and served in various Army hospitals, including the Sternberg General, Chickamauga Park, Ga., Simpson General Hospital, Fort Monroe, Va., and the Letterman General Hospital, San Francisco, Calif. He was a member of the Army Board for Study of Tropical Diseases in Manila, P. I., 1906–07, and taught Bacteriology and Parasitology at the Army Medical School in Washington for several years. He served some time as Director of Laboratories at the Army Medical School and was the recipient of the Distinguished Service Medal.

Colonel Craig was Editor of the American Journal of Tropical Medicine and Associate Editor of the American Journal of Syphilis and the Journal of Parasitology. He was the author of numerous books and articles dealing with Parasitology and Malaria, his most recent publication being "Laboratory Diagnosis of Protozoan Diseases," second edition, published by Lea & Febiger in 1948. In 1931 Colonel Craig retired from the Army and became Professor and Head of the Department of Tropical Medicine at Tulane University of Louisiana School of Medicine, New Orleans. He became Emeritus Professor in 1939. He was a Past President of the American Society of Tropical Medicine, a Life Member of the American Society of Parasitology, and became a Fellow of the American College of Physicians in 1927. He received many honors, and was an active member of many other distinguished societies.

DR. JOHN GRAY GAGE

Dr. John Gray Gage, M.D., F.A.C.P., Arcadia, Calif., was born in Cambridge Springs, Pa., August 15, 1882, and died November 18, 1950, at the age of 68.

He graduated from the University of Michigan Medical School in 1908, and remained there as an Assistant in Internal Medicine until 1909, when he took a similar appointment at Tulane University of Louisiana School of Medicine. From 1910 to 1912, he was Assistant in Physiology at Tulane, but then returned to the University of Michigan Medical School as Instructor in Pharmacology and Therapeutics, holding that post until 1916. He entered the practice of medicine in Akron, Ohio, and was on the staff of the City Hospital there. Later, with the advent of poor health, which confined him to his home, from 1933, he moved to Arcadia, Calif., and thereafter lived in retirement.

He was elected a Fellow of the American College of Physicians in 1926.

DR. GEORGE BURTON GILBERT

George Burton Gilbert, A.B., M.D., F.A.C.P., was born in Thomaston, Conn., September 28, 1881. He died suddenly of a coronary occlusion on April 6, 1951.

Dr. Gilbert obtained his premedical education at Yale University, receiving the A.B. degree in 1903. His M.D. degree in 1908 was obtained from the Johns Hopkins University School of Medicine. He interned at the Hartford Hospital in Hartford, Conn. Shortly thereafter he broke down with pulmonary tuberculosis, during the course of which he moved to Colorado Springs where, upon recovery, he took residency training at the Cragmor Sanatorium.

In addition to a real interest in clinical work, Dr. Gilbert was active in research and teaching having to do with tuberculosis. From 1913 to 1920 he served as Director of the Webb Tuberculosis Research Laboratory, and from 1920 to 1928 he was Secretary and Director of the Colorado School of Tuberculosis. Since its establishment in 1925, he was intimately associated with the Colorado Foundation for Research in Tuberculosis, serving as Associate Research Director during most of this time. All of the principal hospitals in Colorado Springs—notably, Glockner Sanatorium and Hospital, Sunnyrest Sanatorium, Beth-El General Hospital, National Methodist Episcopal Sanatorium for Tuberculosis and the St. Francis Hospital and Sanatorium—counted Dr. Gilbert as an active staff member.

Dr. Gilbert obtained Fellowship in the College in 1931. He was a member of the National Tuberculosis Association, the National Association of Clinical Pathology, the Society of American Bacteriologists, the American Association of Immunologists and the American Medical Association and its allied societies. He was a Diplomate of the American Board of Internal Medicine.

Dr. Gilbert's mark on Colorado medicine and upon research in tuberculosis is one that will stand for many years to come, and his death is a distinct loss to the American College of Physicians as well as to the Colorado community.

WARD DARLEY, M.D., F.A.C.P.,
Governor for Colorado

DR. MOSES GROSS

Moses Gross, B.S., M.D., of Brooklyn, N. Y., was born July 21, 1897, and died January 7, 1951, of coronary thrombosis.

He received his B.S. degree from the College of the City of New York and his M.D. degree from the Jefferson Medical College of Philadelphia in 1923. After his internship at the Beth-El Hospital he was on the medical staff of that hospital until the time of his death. He was an associate in medicine at the Beth-El Hospital since 1936 and served as chief of the thyroid clinic from 1928 to 1941, and was on the staff of the Jewish Sanitarium and Hospital for Chronic Diseases. During World War II he served as Examiner for Selective Service.

Dr. Gross did postgraduate work at Columbia University College of Physicians and Surgeons, the Long Island College of Medicine, and at Temple University School of Medicine in Philadelphia.

He was a member of the Brooklyn Society of Internal Medicine, a Fellow of the American Medical Association and a member of his county and state societies. He was a Diplomate of the American Board of Internal Medicine and was elected an Associate of the American College of Physicians in 1950.

J. SCHWARTZ, M.D., F.A.C.P.

DR. WALLACE TAYLOR PARTCH

Wallace Taylor Partch, M.D., was born in China on February 16, 1899, and died on April 4, 1951, from a primary mesothelioma of the peritoneum.

Dr. Partch received his preliminary education at Oberlin College, qualifying for the A.B. degree in 1921. He graduated from Rush Medical College in 1926, and interned at Wesley Memorial Hospital in Chicago. He went to the Mayo Clinic for his postgraduate training where he remained from 1927 to 1930. Dr. Partch began his medical practice in Oakland at that time, and became one of the leading internists of the Oakland and Berkeley area. He was looked upon with great esteem by all his associates, and as a reward for this esteem he was made Chief of Staff and Chief of Internal Medicine at the Herrick Memorial Hospital in Berkeley. He was also on the staff of the Alameda County, Samuel Merritt, and Peralta Hospitals.

Dr. Partch was a member of the Alameda and Contra Costa Counties Medical Societies, a member of the Pan-American Medical Association and a charter member of the California Society of Internal Medicine. He also held a membership in the California Medical Association, and in the American Medical Association. He was a Diplomate of the American Board of Internal Medicine, and was elected an Associate of the American College of Physicians in 1947.

STACY R. METTIER, M.D., F.A.C.P.,
Governor for Northern California

DR. THEODORE NEWELL RAFFERTY

Theodore Newell Rafferty, an Associate of the American College of Physicians since 1947, died April 8, 1951, in Ochsner Foundation Hospital, New Orleans, La. of subacute bacterial endocarditis and complications.

Dr. Rafferty was born in Robinson, Ill., April 21, 1908. He received his B.S. degree from the University of Illinois in 1929, his M.D. degree from the University of Illinois College of Medicine in 1933, and served his internship at the Illinois Central Hospital, Chicago.

He became intensely interested in diseases of the chest early in his professional career, serving on the staff of the Wm. H. Maybury Sanatorium, Northville, Mich., for a period of three years. He then was appointed Director of the Division of Chest Diseases, Veterans Administration Hospital, New Orleans. He was also a lecturer in the Medical Department of Tulane University of Louisiana School of Medicine.

After resting for a year he became affiliated with the Eastern North Carolina Tuberculosis Sanatorium, Wilson, N. C., where he served until compelled to resign in July, 1950, because of illness.

Dr. Rafferty was the author of "Artificial Pneumothorax in Pulmonary Tuberculosis," published by Grune & Stratton in 1944.

He was a member of the Wilson County, North Carolina State, Orleans Parish, and Louisiana State Medical Societies, as well as the American Medical Association, the American College of Chest Physicians, the American Trudeau Society, the National Tuberculosis Association, and others.

It may be truly said of Dr. Rafferty that he was a "kindly gentleman" with no enemies, and that the study of medicine in its broader sense was at once his vocation and avocation. Although passing at the early age of 42 years, he left his footprints in the sands of time and demonstrated what may be done with the combination of a brave spirit and a frail body. He left a host of friends, both within and without the profession, who will long cherish his memory.

WILLIAM C. BLAKE, M.D., F.A.C.P.,
Governor for Florida

DR. JOHN AUGUSTINE SWEENEY

John Augustine Sweeney, Fellow of the College for seventeen years, died in the Philadelphia General Hospital on February 14, 1951. It was in this institution that he received his early training as a rotating interne and resident in medicine, and later on earned the commendation of his colleagues and students as an assistant physician and instructor in medicine for his medical alma mater.

He was born on November 20, 1895, in what was then known as South Bethlehem, Pa. His parents, however, moved to Lansford in the same state when he was a mere boy. He successively attended the local schools of that community, Wyoming

Seminary, the University of Pennsylvania as a pre-medical student and finally received his degree in medicine from the University of Pennsylvania School of Medicine in 1921.

About this time the electrocardiograph was coming to the fore as an instrument for clinical investigation and patient study. So it was that young Sweeney, having familiarized himself with electrocardiographic technics, turned very reasonably, as many others did then, to diseases of the heart for special endeavor. Subsequently, he achieved a well deserved reputation in this field and served as cardiologist for the Misericordia Hospital and the White Haven Sanatorium. At the same time he was an attending physician to both of these institutions.

He treasured his Fellowship in the American College of Physicians and, almost with equal satisfaction, his membership in the American Heart Association, the National Tuberculosis Association, the Laennec Society, and his Fellowship in the College of Physicians of Philadelphia. He was certified in Internal Medicine. He was a member of his county and state medical societies as well as the American Medical Association.

By virtue of the opportunities afforded in the White Haven Sanatorium and the friendship and inspiration of Dr. Lawrence Flick, our late Fellow achieved a specialistic ability not only in the field of pulmonary tuberculosis but also in the diagnosis and treatment of diseases of the chest generally. His tenure of service in the sanatorium was marked by the ultimate satisfaction of his patients and colleagues on the staff as well.

It was, however, on one of his visits to White Haven in 1937 that he tripped and fell on a railroad track and probably acquired a high cervical dislocation. This unfortunate accident seems to date the real beginning of a marked motor and sensory disability which limited his professional activity for the most part to office practice. There were, to be sure, some excursions to the bedside of patients, to hospitals, to the classroom, and to devotions, always, however, with obvious effort. There was the curtailment of his literary production and his attendance at medical meetings, but there were always his medical journals and his interest in philately.

In spite of great handicaps, he continued on most courageously without ever repining at his lot, always cheerful, never depressed, and never losing his interest in medicine, his patients, family, and people generally. The cross became increasingly heavy, however, as the years passed by and so recourse was taken in an operative venture, to be followed some time later by the fracture of a humerus during the practice of some physiotherapeutic procedure. But all was of no avail and he finally succumbed just as he had lived, bravely, unselfishly, and serving as an inspiration to all who knew him.

TRUMAN G. SCHNABEL, M.D., F.A.C.P.